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(54) Title: TREATMENTS FOR NEUROGENETIC DISORDERS, IMPULSE CONTROL DISORDERS, AND WOUND HEALING

(57) Abstract: The subject invention provides methods and compositions for the treatment of neurogenetic disorders, particularly DSM-IV impulse control disorders such as intermittent explosive disorder, kleptomania, pyromania, pathologic gambling, trichotillomania, and other impulse control disorders such as compulsive buying and problematic Internet use. In a preferred embodiment, the subject invention provides methods for treating or controlling symptons associated with ADHD or PWS comprising the administration of therapeutically effective amounts of compositions containing compounds of the formulas I-V. In another embodiment, the subject invention provides for methods of promoting wound healing comprising the administration of a therapeutically effective amount of a composition comprising the compounds of formulas I-V. Compositions may administered to a wound site via a salve, ointment, or as a component of a bandage or bioadhesive applied to the site of injury. The invention also provides therapeutically effective compositions comprising one or more of the compounds of formulas I-V.

DESCRIPTION

TREATMENTS FOR NEUROGENETIC DISORDERS, IMPULSE CONTROL DISORDERS, AND WOUND HEALING

Cross-Reference to Related Application

The present claims the benefit of U.S. Provisional Application No. 60/250,113, filed November 30, 2000, which is hereby incorporated by reference herein in its entirety, including any figures, tables, or drawings.

Background of the Invention

[0001] As many as one-third of the approximate 3,000 known genetic disorders are believed to have important neurological involvement. Individually, most genetic disorders are of low incidence in the general population; however, collectively they represent an enormous burden on affected individuals, their families, and society. Many neurogenetic disorders manifest themselves early in life leading to either a premature death or to lifelong disability with significant attendant psychological and economic hardships.

[0002] Examples of these types of disorders include: (1) Hereditary ataxias and related disorders such as Friedreich ataxia, ataxia telangiectasia, olivopontine cerebellar degeneration, Ramsay Hunt syndrome, abetalipoproteinemia, Machado-Joseph disease, and familial spastic paraparesis; (2) Movement disorders such as Juvenile Huntington disease, the dystonias including blepharospasm and spasmodic torticolis, tremor, myoclonus, and Hallervorden-Spatz disease; (3) Phakomatoses, or neurocutaneous syndromes such as neurofibromatosis, tuberous sclerosis, Sturge-Weber, and Von Hippel-Landau disease; (4) Mitochondrial encephalomyopathies such as the MELAS syndrome, Kearns-Sayre, and Leigh disease; (5) Hereditary disorders of nerve and muscle such as infantile spinal muscular atrophy, Charcot-Marie-Tooth disease, hereditary sensory and autonomic neuropathies, genetic myasthenic syndromes, metabolic myopathies, muscular dystrophies, and myotonias.

[0003] There are numerous other neurological disorders that are also believed to result from genetic abnormalities such as the Laurence-Moon-Bardet-Biedl, Aicardi, Sjogren-Larsson, Prader-Willi and Angelman syndromes.

[0004] In addition to those diseases that have a recognizable pattern of inheritance, there are many other neurological disorders that seem to have, in some cases, a familial basis. These may well represent neurogenetic disorders with multifactorial etiology. Such diseases can be as diverse as disorders of defective cellular migration (such as lissencephaly, heterotopias), neural tube defects, congenital hydrocephalus, myoclonic epilepsy, attention deficit hyperactivity disorder (ADHD), and narcolepsy.

[0005] It is estimated that ADHD affects about 4% to 6% of the U.S. population. ADHD is not limited to children and is a chronic lifetime disease. Approximately one-half to two-thirds of children with ADHD will continue to have significant problems in adulthood and experience difficulties which impact employment, familial, and social relationships.

[0006] According to the DSM-IV (the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) some common symptoms of ADHD include: (1) often fails to give close attention to details or makes careless mistakes; (2) often has difficulty sustaining attention to tasks; (3) often does not seem to listen when spoken to directly; (4) often fails to follow instructions carefully and completely; (5) losing or forgetting important things; (6) feeling restless, often fidgeting with hands or feet, or squirming; (7) running or climbing excessively; (8) often talks excessively; (9) often blurts out answers before hearing the whole question; and (10) often has difficulty awaiting turn. It should be kept in mind that the exact nature and severity of ADHD symptoms varies from person to person however. Approximately one-third of people with ADHD do not have the hyperactive or overactive behavior component.

[0007] To meet diagnostic criteria, these behaviors must be excessive, long-term, and pervasive. The behaviors must appear before age 7, and continue for at least 6 months. A crucial element requires that the behaviors must create a real handicap in at least two areas of a person's life, such as school, home, work, or social settings. These criteria set ADHD apart from the "normal" distractibility and impulsive behavior of childhood, or the effects of the hectic and overstressed lifestyle prevalent in our society.

[0008] There are no reports in the literature of topiramate specifically used to treat deficits in attention and concentration. Carbamazepine (Tegretol) has been reported to be useful for the treatment of patients experiencing sudden confusion and depression. Within weeks of initiating treatment, the patients experienced fewer incidences of sudden confusion

and depression, and an increase in attention and focus. Persinger, M.A., "Subjective improvement following treatment with carbamazepine (Tegretol) for a subpopulation of patients with traumatic brain injuries", *Percept Mot Skills* 90:37-40 (2000). Carbamazepine has also been shown to be effective in treating children with features of ADHD. Silva, R.R.; Munoz, D.M.; Alpert, M., "Carbamazepine use in children and adolescents with features of attention-deficit hyperactivity disorder: a meta-analysis", *J Am Acad Child Adolesc Psychiatry* 35:352-358 (1996). In some patients, with or without intellectual disability, being treated for refractory partial epilepsy, gabapentin is an equally effective add-on medication. Mikati, M.A.; Choueri, R.; Khurana, D.S.; *et al.*, "Gabapentin in the treatment of refractory partial epilepsy in children with intellectual disability", *J Intellect Disabil Res* 42:57-62 (suppl. 1, 1998). Three dementia patients are noted in the literature to have received topiramate in a retrospective chart review of 58 consecutive psychiatric patients receiving topiramate. Marcotte, D., "Use of topiramate, a new anti-epileptic as a mood stabilizer", *J Affect Disorder* 50:245-251 (1998). "Improvement" was rated by a Likert scale from 'worse,' to 'no change,' to 'minimally improved,' to 'moderately improved,' to 'markedly improved.' The three patients with dementia are described to have 'moderate' or 'marked' improvement when on topiramate. The author of this chart review hypothesized that topiramate may have some anti-psychotic effect.

[0009] While there have been no reported efforts to use topiramate for the treatment of impulsivity, there have been a limited number of publications reporting the effects of anti-convulsant treatment on impulsivity (or measures of impulsivity). These references tend to show no change or worsening of impulsivity with anti-convulsant treatment. For example, one large study showed no overall effect on measures of impulsivity of anti-convulsant medication in epileptic children (Mitchell, W.G.; Zhou, Y.; Chavez, J.M.; Guzman, B.L., "Reaction time, attention, and impulsivity in epilepsy", *Pediatr Neurol* 8:19-24 (1992)) and another large study showed, at higher total serum levels of anti-convulsant medication in children with epilepsy, more impulsive errors on complex reaction time testing (Mitchell, W.G.; Zhou. Y.; Chavez, J.M.; Guzman, B.L., "Effects of anti-epileptic drugs on reaction time, attention, and impulsivity in children", *Pediatrics* 91:101-105 (1993)). It is notable that both of these studies focused on children with epilepsy.

[0010] A case report from 1987 described carbamazepine being useful for intermittent explosive disorder in a patient with Prader-Willi Syndrome (Gupta, B.K.; Fish,

D.N.; Yerevanian, B.I., "Carbamazepine for intermittent explosive disorder in a Prader-Willi syndrome patient", *J Clin Psychiatry* 48:423 (1987)). Carbamazepine has also been reported useful in the treatment of pathological gambling (Haller, R.; Hinterhuber, H., "Treatment of pathological gambling with carbamazepine", *Pharmacopsychiatry* 27:129 (1994)). There are also reports in the literature of divalproex being effective for explosive mood and mood lability (Donovan, S.J.; Stewart, J.W.; Nunes, E.V.; Quitkin, F.M.; Parides, M.; Daniel, W.; Susser, Klein D.F., "Divalproex treatment for youth with explosive temper and mood lability: a double-blind, placebo-controlled crossover design", *Am J Psychiatry* 157:818-820 (2000)) and for a patient with kleptomania and mixed mania (Kmetz, G.F.; McElroy, S.L.; Collin, D.J., "Response of kleptomania and mixed mania to valproate", *Am J Psychiatry* 154:580-581 (1997)).

[0011] Prader-Willi Syndrome (PWS) is a neurogenetic multisystem disorder characterized by infantile hypotonia, mental retardation, short stature, hypogonadism, dysmorphic features, and hyperphagia with a high risk of obesity. Also very common in PWS are behavioral and psychiatric manifestations. These include self-injury (e.g. gouging, nail biting, and skin picking), explosive outbursts, oppositional behavior, obsessive ruminations, and compulsive behaviors including hoarding, counting, and arranging. PWS is typically a sporadic condition, which usually results from a deletion in chromosome 15q11-q13 or maternal uniparental disomy of chromosome 15. Glenn, C.G.; Driscoll, D.J.; Thomas, P.Y.; Nicholls, R.D., "Genomic imprinting: potential function and mechanisms revealed by the Prader-Willi and Angelman syndromes", *Mol Hum Reprod* 3:321-332 (1997).

[0012] PWS is also a relatively common genetic condition with an estimated prevalence of approximately 1/10,000 to 1/25,000. Glenn, C.G.; Driscoll, D.J.; Thomas, P.Y.; Nicholls, R.D., "Genomic imprinting: potential function and mechanisms revealed by the Prader-Willi and Angelman syndromes", *Mol Hum Reprod* 3:321-332 (1997). It was first described in 1956 (Prader, A.; Labhart, A.; Willi, H., "Ein Syndrome von adipositas, Kleinwuchs, Kryptorchismus und Oligophrenic nach myoteniertigem zusland in neugeborenanalter", *Schwiez Med Wschr* 86:1260-1 (1956)), and the physical problems (such as the obesity related cardiovascular diseases, diabetes mellitus, etc.) and behavioral problems result in the major causes of morbidity and mortality. Martin, A.; Matthew, S.; Koenig, K.; *et al.*, "Prader-Willi syndrome", *Am J Psychiatry* 155:1265-1273 (1998).

[0013] Treatment for the physical, behavioral, and psychological problems associated with PWS is complex. The mainstay of treatment for behavioral problems including hyperphagia is behavioral modification including strategies such as token economies or star systems. Dykens, E.M.; Hodapp, R.M., "Treatment issues in genetic mental retardation syndromes", *Professional Psychology: Research and Practice* 28:263-270 (1997). Additionally, medication management of individuals with PWS has been demonstrated to have benefit. Growth hormone therapy in children with PWS can increase muscle tone and enhance growth. Carrel, A.L.; Myers, S.C.; Whitman, B.Y.; *et al.*, "Growth hormone improves body composition, fat utilization, physical strength and agility, and growth in Prader-Willi syndrome: A controlled study", *J Pediatr* 134:215-221 (1999); Lindgren, A.C.; Hagenas, L.; Muller, J.; *et al.*, "Effects of growth hormone treatment on growth and body composition in Prader-Willi syndrome: a preliminary report", *The Swedish National Growth Hormone Advisory Group. Acta Paediatr Suppl* 423:60-62 (1997). Therefore, growth hormone can help to normalize body habitus. Martin, A.; Matthew, S.; Koenig, K.; *et al.*, "Prader-Willi syndrome", *Am J Psychiatry* 155:1265-1273 (1998); Carrel, A.L.; Myers, S.C.; Whitman, B.Y.; *et al.*, "Growth hormone improves body composition, fat utilization, physical strength and agility, and growth in Prader-Willi syndrome: A controlled study", *J Pediatr* 134:215-221 (1999); Lindgren, A.C.; Hagenas, L.; Muller, J.; *et al.*, "Effects of growth hormone treatment on growth and body composition in Prader-Willi syndrome: a preliminary report", *The Swedish National Growth Hormone Advisory Group. Acta Paediatr Suppl* 423:60-62 (1997). In terms of obesity, the anorectic fenfluramine was shown to be helpful for weight loss and aggressive behavior in PWS utilizing a double-blind placebo-controlled trial. Selikowitz, M.; Sunman, J.; Pendergast, A.; *et al.*, "Fenfluramine in Prader-Willi syndrome: a double-blind, placebo controlled trial", *Arch Dis Childhood* 65:112-114 (1990). Unfortunately due to cardiovascular consequences, fenfluramine is not now currently available. There are few studies of anorectic agents in PWS and anecdotal reports have been discouraging in terms of their benefits. Martin, A.; Matthew, S.; Koenig, K.; *et al.*, "Prader-Willi syndrome", *Am J Psychiatry* 155:1265-1273 (1998).

[0014] Pathological skin picking (PSP) is a severe and chronic psychiatric and dermatologic problem with an average age of onset around 15 years of age and mean duration of illness of 21 years. Keuthen, W.S.; Deckersbach, T.; Engelhard, I.M.; *et al.*, "Self-injurious skin picking: clinical characteristics and comorbidity", *J Clin Psychiatry* 60:454-

459 (1999). PSP can lead to significant suffering, dysfunction, and disfigurement. Ko, S.M., "Under-diagnosed psychiatric syndrome II: Pathologic skin picking", *Ann Acad Med Singapore* 28:557-559 (1999). Furthermore, there is often psychiatric comorbidity. Keuthen, W.S.; Deckersbach, T.; Engelhard, I.M.; *et al.*, "Self-injurious skin picking: clinical characteristics and comorbidity", *J Clin Psychiatry* 60:454-459 (1999). PSP is often considered an obsessive compulsive spectrum disorder (Goldsmith, T.D.; Shapira, N.A.; Phillips, K.A.; *et al.*, "Obsessive Compulsive Spectrum Disorders"; in: Swinson, R.P.; Antony, M.M.; Rachman, S.; Richter, M.A. (Eds)., *Obsessive-Compulsive Disorder: Theory, Research, and Treatment*, Guilford Publications, New York, pp.397-425 (1998)) and, as such, there are several reports of serotonin receptor inhibitors (SSRI) medication being helpful. Ko, S.M., "Under-diagnosed psychiatric syndrome II: Pathologic skin picking", *Ann Acad Med Singapore* 28:557-559 (1999).

[0015] The literature points to topiramate having a negative impact on cognitive functioning including impaired concentration, attention, memory, slowed thinking, word finding, and verbal fluency. Thompson, P.J.; Baxendale, S.A.; Duncan, J.S.; *et al.*; "Effects of topiramate on cognitive function", *J Neurol Neurosurg Psychiatry* 69:636-641 (2000); Privitera, M.; Fincham, R.; Penry, J.; *et al.*, "Topiramate placebo-controlled dose-ranging trial in refractory partial epilepsy using 600-, 800-, and 1,000-mg daily dosages", *Topiramate YE Study Group. Neurology* 46:1678-1683 (1996); Crawford, P., "An audit of topiramate use in a general neurology clinic", *Seizure* 7:207-211 (1998); Jones, M.W., "Topiramate—safety and tolerability", *Can J Neurol Sci* 25:S13-15 (1998); Burton, L.A.; Harden, C., "Effect of topiramate on attention", *Epilepsy Res* 27:29-32 (1997); Martin, R.; Kuzniecky, R.; Ho, S. "Cognitive effects of topiramate, gabapentin, and lamotrigine in healthy young adults", *Neurology* 52:321 (1999); Fraught, E.; Wilder, B.J.; Ramsay, R.E.; *et al.*, "Topiramate placebo-controlled dose-ranging trial in refractory partial epilepsy using 200-, 400-, and 600-mg daily dosages," *Neurology* 46:1684-1690 (1996); and Rosenfeld, W.E.; Liao, S.; Kramer, L.D.; *et al.*, "Comparison of the steady-state pharmacokinetics of topiramate and valproate in patients with epilepsy during monotherapy and concomitant therapy", *Epilepsia* 38:324-333 (1997). A few studies have systematically looked at cognitive changes using neuropsychological testing. In one study (Burton, L.A.; Harden, C., "Effect of topiramate on attention", *Epilepsy Res* 27:29-32 (1997)), 10 adult patients with epilepsy were evaluated weekly for up to 13 weeks via a digit span test. In 4 patients, there was an inverse correlation

between topiramate does and test performance. In another study, healthy volunteers were treated with topiramate, gabapentin, or lamotrigine for 4 weeks. Impaired cognitive functioning (attention and word fluency) was seen in the topiramate treated subjects and not in gabapentin or lamotrigine in these healthy young adults. Martin, R.; Kuzniecky, R.; Ho, S. "Cognitive effects of topiramate, gabapentin, and lamotrigine in healthy young adults", *Neurology* 52:321 (1999). Finally, in a recent study of 18 epilepsy patients treated with topiramate and receiving repeat neuropsychological assessments, patients on topiramate showed significant deterioration in many cognitive domains, including verbal IQ, verbal fluency, and verbal learning. Thompson, P.J.; Baxendale, S.A.; Duncan, J.S.; *et al.*; "Effects of topiramate on cognitive function", *J Neurol Neurosurg Psychiatry* 69:636-641 (2000). Improvement in verbal fluency, verbal learning, and digit span increased in patients where topiramate was withdrawn or reduced.

[0016] The subject invention has, surprisingly, found improvements in impulsivity control, without negative effects on attention and concentration, in patients treated with topiramate. These observations are unexpected and novel.

Brief Summary of the Invention

[0017] The subject invention provides methods and compositions for the treatment of neurogenetic disorders, particularly DSM-IV impulse control disorders such as intermittent explosive disorder, kleptomania, pyromania, pathologic gambling, trichotillomania, and other impulse control disorders such as compulsive buying and problematic Internet use. In a preferred embodiment, the subject invention provides methods for treating or controlling symptoms associated with ADHD or PWS comprising the administration of therapeutically effective amounts of compositions containing compounds of the formulas I-V. In another embodiment, the subject invention provides for methods of promoting wound healing comprising the administration of a therapeutically effective amount of a composition comprising the compounds of formulas I-V. Compositions are administered to a wound site via a salve, ointment, or as a component of a bandage or bioadhesive applied to the site of injury. The invention also provides therapeutically effective compositions comprising one or more of the compounds of formulas I-V.

Brief Description of the Drawings

[0018] The patent or application file contains at least one drawing executed in color. Copies of this patent or patent application publication, with color drawing(s), will be provided by the Office upon request and payment of the necessary fee.

[0019] Figures 1, 3, 5, and 7 depict the efficiency ratios of patients treated with topiramate as measured by the Delay Task of the Gordon Diagnostic.

[0020] Figures 2, 4, 6, and 8 depict the total correct responses of patients treated with topiramate as measured by the Vigilance Task of the Gordon Diagnostic.

[0021] Figures 9A-D and 10A-C depict the progression of wound healing in patients treated with topiramate.

[0022] Figures 11A-B: Photographs of improvement in wound healing for Ms. A on topiramate (75 mg/day) at week 4 (Figure 11A) and 150 mg/day topiramate at week 8 (Figure 11B).

[0023] Figures 12A-B: Photographs of improvement for Mr. B. Mr. B. on 25 mg/day topiramate (Figure 12A), Week 1; Mr. B. on 200 mg/day topiramate (Figure 12B), Week 8.

[0024] Figures 13A-B: Photographs of primary SIB lesions. Ms. C. (right breast), baseline (Figure 13A); Ms. C. on 175 mg/day (right breast), Week 8 (Figure 13B).

[0025] Figure 14: Number of ulcerated SIB lesions for Ms. C. as documented by group home staff utilizing systematic full body surveys (* denotes lesions smaller than previous lesions and appearing to result after insect bites).

[0026] Figures 15A-B: Photographic record of Ms. A hair loss at start of treatment (Figure 15A) and during treatment (Figure 15B).

[0027] Figure 16 illustrates the reported reduction in the urge of Ms. A to pull hair.

[0028] Figure 17 represents the improvement in impulse control for Ms. A during treatment using the Gordon Diagnostic System.

[0029] Figure 18 illustrates that Ms. A suffered no significant change in cognitive ability during treatment.

Detailed Disclosure of the Invention

[0030] The subject invention provides methods and compositions for the treatment of neurogenetic disorders, particularly DSM-IV impulse control disorders such as intermittent explosive disorder, kleptomania, pyromania, pathologic gambling, trichotillomania, and other impulse control disorders such as compulsive buying and problematic Internet use. In a preferred embodiment, an individual is treated in methods comprising the administration of therapeutically effective amounts of compositions comprising compounds selected from the group consisting of formulas I-V. In one embodiment, therapeutically effective amounts of topiramate are administered to individuals topically or orally. In another embodiment, compositions comprising one or more of the compounds disclosed in formulas I-V are administered for the control or treatment neurogenetic disorders. In preferred embodiments the neurogenetic disorders include PWS and ADHD.

[0031] Thus, the subject invention provides methods and compositions for the treatment or control of ADHD or PWS. In one embodiment, the subject invention provides methods for controlling symptoms associated with ADHD or PWS comprising the administration of therapeutically effective amounts of compositions containing compounds of the formulas I-V. One embodiment of the invention provides therapeutically effective compositions comprising one or more of the compounds of formulas I-V and acceptable carriers.

[0032] In another embodiment, the subject invention provides methods of promoting wound healing comprising the administration of a therapeutically effective amount of a composition comprising the compounds of formulas I-V to an individual having a wound. In one embodiment, compositions are topically administered to a wound. The compositions may take the form of a salve, ointment, or aerosol applied to the site of injury. Alternatively, the compositions may be administered to the wound site as a component of a bandage or transdermal patch. In these instances, the compositions may be an integral component of the bandage or transdermal patch and are thereby applied to the wound site. In another embodiment, therapeutically effective amounts of the compounds comprising

formulas I-V are incorporated into bioadhesive compositions useful in wound closure. In yet another embodiment, therapeutically effective amounts compositions comprising the compounds of formulas I-V are administered orally.

[0033] As the subject invention provides methods of promoting wound healing or controlling impulsive behavior in an individual, the subject invention provides methods having both human and veterinary utility. The term "individual" includes animals of avian, mammalian, or reptilian origin. Mammalian species which benefit from the disclosed methods include, and are not limited to, apes, chimpanzees, orangutans, humans, monkeys; domesticated animals (pets) such as dogs, cats, guinea pigs, hamsters, Vietnamese pot-bellied pigs, rabbits, and ferrets; domesticated farm animals such as cows, buffalo, bison, horses, donkey, swine, sheep, and goats; exotic animals typically found in zoos, such as bear, lions, tigers, panthers, elephants, hippopotamus, rhinoceros, giraffes, antelopes, sloth, gazelles, zebras, wildebeests, prairie dogs, koala bears, kangaroo, opossums, raccoons, pandas, giant pandas, hyena, seals, sea lions, and elephant seals. Reptiles include, and are not limited to, alligators, crocodiles, turtles, tortoises, snakes, iguanas, and/or other lizards. Avian species include, and are not limited to, chickens, turkeys, pigeons, quail, parrots, macaws, dove, Guinea hens, lovebirds, parakeets, flamingos, eagles, hawks, falcons, condor, ostriches, peacocks, ducks, and swans. Therefore, the subject invention provides methods of controlling the impulse of an individual to scratch, pick, lick, or otherwise cause self-injury by repeated mechanical irritation of an injured area.

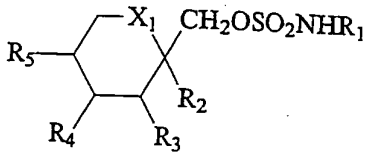
[0034] Bandages and wound dressings incorporating materials to promote wound healing are well known in the art (see, for example, U.S. Patent Nos. 6,143,037; 6,142,982; 6,136,341; 6,132,759; 6,124,273; 6,096,709; 6,093,388; 6,087,549; 6,051,249; 6,033,684; 6,025,150; 6,022,556; 5,998,692; 5,989,577; 5,981,606; 5,977,428; RE36,370; 5,972,332; 5,968,001; 5,960,795; 5,955,430; 5,914,125; 5,902,600; 5,897,516; 5,876,743; 5,874,479; 5,863,938; 5,856,364; 5,856,245; 5,834,432; 5,807,341; 5,807,300; 5,804,213; 5,780,048; 5,759,570; 5,735,812; 5,716,935; 5,716,337; 5,713,842; 5,707,647; 5,705,477; 5,692,302; 5,685,834; 5,674,912; 5,667,501; 5,663,208; 5,662,924; 5,662,904; 5,658,957; 5,658,956; 5,652,274; 5,648,380; 5,646,190; 5,641,814; 5,633,285; 5,632,727; 5,629,292; 5,614,561; 5,610,148; 5,603,946; 5,602,183; 5,578,022; 5,571,521; 5,525,335; 5,522,794; 5,520,926; 5,519,020; 5,512,291; 5,512,041; 5,507,775; 5,578,310, each of which is incorporated by reference in its entirety).

[0035] Bioadhesives incorporating materials to promote wound healing are well known in the art (see, for example, U.S. Patent Nos. 5,981,606; 5,874,479; 5,863,938; 5,856,364; 5,692,302; 5,674,912; 5,663,208; 5,658,957; 5,658,956; 5,652,274; 5,648,380; 5,646,190; 5,641,814; 5,633,285; 5,631,019; 5,614,561; 5,602,183; 5,578,310, each of which is incorporated by reference in its entirety).

[0036] Compounds of formulas I-V are anti-epileptic compounds, which are highly effective anti-convulsants. The compounds useful in the practice of the instant invention include the individual isomers, analogs, and homologs of the disclosed anti-convulsant compounds. Racemic mixtures, as well as the isolated enantiomeric forms, of the compounds can also be used in the practice of the subject invention.

[0037] In addition, the compounds useful for the practice of the subject invention include pharmaceutically acceptable salts, for example; alkali metal salts, such as sodium or potassium, ammonium salts, dialkyammonium salts, trialkylammonium salts, tetraalkylammonium salts, and tromethamine salts. Hydrates and other solvates of the compounds are also included within the scope of the compounds useful in the practice of this invention.

[0038] One such compound is taught and disclosed in U.S. Pat. No. 4,513,006, hereby incorporated by reference in its entirety. 2,3:4,5-bis-O-(1-methylethylidene)-β-D-fructopyranose sulfamate, known as topiramate, has been demonstrated in clinical trials of human epilepsy to be effective as adjunctive therapy or as monotherapy in treating simple and complex partial seizures and secondarily generalized seizures. Other useful compounds include those described by formula I, including (tetrahydro-2H-pyran-2-yl)methane sulfamate, and 2,3:4,5-bis-O-(1-methylethylidene)-β-D-fructopyranose methylsulfamate



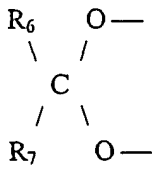
(Formula I)

wherein

X_1 is CH_2 or oxygen;

R_1 is hydrogen or alkyl; and

[0039] R_2, R_3, R_4, and R_5 are independently hydrogen or lower alkyl and, when X_1 is CH_2, R_4, and R_5 may be alkene groups joined to form a benzene ring and, when X_1 is oxygen, R_2 and R_3 and/or R_4 and R_5 together may be a methylenedioxy group of the following formula:



wherein R_6 and R_7 are the same or different and are hydrogen, lower alkyl or are alkyl and are joined to form a cyclopentyl or cyclohexyl ring.

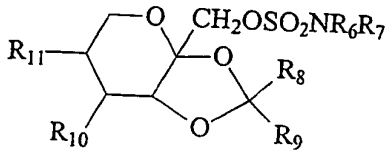
[0040] For compounds of formula I, R_1 may be hydrogen or an alkyl of about 1 to 4 carbons, such as methyl, ethyl, and isopropyl. Alkyl includes straight and branched chain alkyl. For compounds of formula I, Alkyl groups for R_2, R_3, R_4, R_5, R_6, and R_7 are of about 1 to 3 carbons and include methyl, ethyl, isopropyl and N-propyl.

[0041] When X_1 is CH_2, R_4 and R_5 may combine to form a benzene ring fused to the 6-membered X_1-containing ring, *i.e.*, R_4 and R_5 are defined by the alkatrienyl group =CH—CH=CH—CH=.

[0042] In one embodiment, X_1 is oxygen and both R_2 and R_3 and R_4 and R_5 together are methylenedioxy groups of the formula wherein R_6 and R_7 are both hydrogen, both alkyl or combine to form a spiro cyclopentyl or cyclohexyl ring, in particularly where R_6 and R_7 are both alkyl such as methyl. In another embodiment, X_1 is CH_2 and R_4 and R_5 are joined to form a benzene ring. Another embodiment provides compounds of formula (I) wherein both R_2 and R_3 are hydrogen.

[0043] Other compounds (formulas II-VI) and compositions useful in the practice of the subject invention may be found in the teachings of U.S. Pat. Nos. 5,384,327, 5,498,629, 5,654,461, 5,892,088, and 6,071,537, each of which is incorporated by reference in their entireties.

[0044] These compounds include those provided by the structure:



(Formula II)

wherein R_6 and R_7 may be the same or different and are selected from any of hydrogen or C_1 to C_4 alkyl. In one embodiment, R_6 and R_7 are each hydrogen.

[0045] R_8 and R_9 may be the same or different and are selected from any of hydrogen or C_1 to C_4 alkyl. In one embodiment, R_8 and R_9 are each C_1 to C_4 alkyl.

[0046] R_{10} and R_{11} may be the same or different and are selected from any of azido, halogen, hydroxyl, sulfamoyl (H_2NSO_2O), C_1 to C_4 alkoxy, C_1 to C_4 alkyl thiocarbonate (RSC(O)O), C_1 to C_4 alkyl carbonate (ROC(O)O), or C_1 to C_4 alkyl carboxylate (RC(O)O), wherein R is C_1 to C_4 alkyl. In one embodiment, R_{10} and R_{11} are selected from any of C_1-C_4 alkyl thiocarbonate, halogen or hydroxyl.

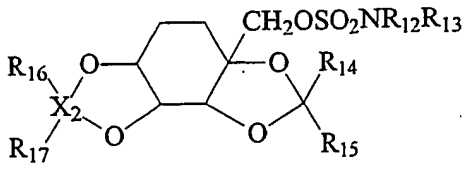
[0047] For compounds of formula II, the terms alkyl and alkoxy include straight and branched chains. For example, alkyl radicals include methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, and t-butyl. Halogen includes bromine, chlorine, fluoride and iodine.

[0048] Preferred compounds of the formula (II) are those wherein the pyran ring is in the L-sorbopyranose absolute configuration. Particularly preferred compounds of formula (II) are those wherein the pyran ring is in the L-sorbopyranose absolute configuration, R_6 and R_7 are each hydrogen, R_8 and R_9 are each methyl; R_{10} is methyl thiocarbonate ($CH_3SC(O)O$) and R_{11} is halogen; or R_{10} and R_{11} are both halogen; or R_{10} is hydroxyl and R_{11} is halogen. Particularly preferred halogens include bromine, chlorine, and iodine.

[0049] Specific examples of compounds of formula (II) are: (1) 5-deoxy-5-iodo-2,3-O-(1-methylethylidene)-4-[methylthiocarbonyl)]-α-L-sorbopyranose sulfamate, (*i.e.*, where the compound is in the L-sorbopyranose absolute configuration, R_6 and R_7 are hydrogen, R_8 and R_9 are methyl, R_{10} is $CH_3SC(O)O$, and R_{11} is iodine); (2) 4,5-dibromo-4,5-dideoxy-2,3-O-(1-methylethylidene)-α-L-sorbopyranose sulfamate, (*i.e.*, where the

compound is in the L-sorbopyranose absolute configuration, R_6 and R_7 are hydrogen, R_8 and R_9 are methyl, R_{10} and R_{11} are bromine); and (3) 5-chloro-5-deoxy-2,3-O-(1-methylethylidene)-α-L-sorbopyranose sulfamate, (*i.e.*, where the compound is in the L-sorbopyranose absolute configuration, R_6 and R_7 are hydrogen, R_8 and R_9 are methyl, R_{10} is hydroxyl, and R_{11} is chlorine).

[0050] Another compound useful in the practice of the invention is described in Formula III:



(Formula III)

wherein R_{12} and R_{13} are the same or different and are selected from any of hydrogen, alkyl (C_1 to C_6), cycloalkyl (C_3-C_7), allyl, or benzyl. In one embodiment, R_{12} and R_{13} are each hydrogen. R_{14} and R_{15} are the same or different and selected from hydrogen or lower alkyl.

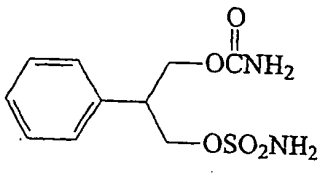
[0051] X_2 may be chosen from carbon (C) or sulfur (S), with the stipulation that when X_2 is carbon, R_{16} and R_{17} are the same or different and are selected from hydrogen or lower alkyl, whereas when X_2 is sulfur one of R_{16} and R_{17} is oxygen and the other is a lone pair of electrons or both R_{16} and R_{17} are oxygen.

[0052] For compounds of formula III, the term alkyl includes straight and branched chains. For example, alkyl radicals include methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, and t-butyl.

[0053] Particularly preferred compounds of formula III are: (1) (1R,2R,3S,4S)-(1,2:3,4-di-O-methylethylidenecyclohexan-1,2,3,4-tetraol-r-yl)methyl sulfamate, (*i.e.*, where R_{12} and R_{13} are hydrogen, R_{14}, R_{15}, R_{16}, and R_{17} are methyl and X_2 is carbon); (2) (1R,2S,3S,4S)-(3,4-O-methylethylidene-1,2-O-sulfonyl-cyclohexan-1,2,3,4-tetraol-4-yl) methyl sulfamate, (*i.e.*, where R_{12} and R_{13} are hydrogen, R_{14} and R_{15} are methyl, R_{16} is oxygen and R_{17} is an electron pair and X_2 is sulfur); and (3) (1R,2S,3S,4S)-(3,4-O-methylethylidene- 1,2-O-sulfonyl-cyclohexan-1,2,3,4-tetraol-4-yl)methyl sulfamate, (*i.e.*,

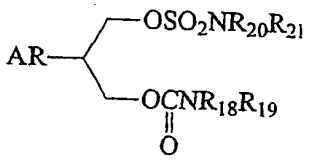
where R_{12} and R_{13} are hydrogen, R_{14} and R_{15} are methyl, R_{16} and R_{17} are both oxygen and X_2 is sulfur).

[0054] Another compound useful in the subject invention is



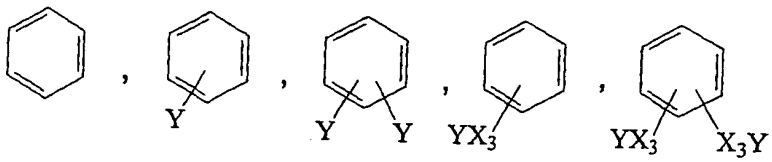
(Formula IV)

[0055] Other compounds useful in the practice of the invention include those of Formula V



(Formula V)

wherein, AR is represented by the following formulas:



[0056] Y is selected from the group consisting of halogens such as F, Cl, Br and I, or trifluoromethyl and alkyl groups containing 1 to 3 carbon atoms when Y alone is attached to the benzene ring; when X_3, which may be S or O, is present, Y is selected from the group consisting of trifluoromethyl and alkyl groups containing 1 to 3 carbon atoms. R_{18}, R_{19}, R_{20}, and R_{21}, may be identical or different and are selected from the group consisting of hydrogen, linear or branched alkyl groups containing 1 to 16 carbon atoms, cyclic alkyl groups containing 3 to 16 carbon atoms and aryl groups containing 6 to 8 carbon atoms, and $NR_{18}R_{19}$ and $NR_{20}R_{21}$, identical or different, each may form a 3 to 7-membered aliphatic cyclic compound together with another nitrogen atom or oxygen atom.

[0057] Compositions useful in the practice of this invention comprise one or more of the compounds of formulas I-V admixed with a pharmaceutical carrier. The compositions may be made according to conventional pharmaceutical compounding techniques. Thus, the carrier may take a wide variety of forms depending on the form of preparation desired for administration, *e.g.*, injection, oral, suppository, topical, or parenteral.

[0058] In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed. Thus, for liquid oral preparations, such as for example, suspensions, elixirs and solutions, suitable carriers and additives include water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like; for solid oral preparations such as, for example, powders, capsules and tablets, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like.

[0059] Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are employed. If desired, tablets may be sugar coated or enteric coated by standard techniques. Suppositories may be prepared, in which case cocoa butter could be used as the carrier.

[0060] For parenterals, the carrier will usually comprise sterile water, though other ingredients, for example, for purposes such as aiding solubility or for preservation, may be included. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed.

[0061] Other compositions useful in the practice of the subject invention include salves, cosmetics, ointments, and the like. Such compositions may be topically applied to a site or incorporated into articles of manufacture including, but not limited to, bandages, adhesive strips for the covering of wounds (*e.g.*, BANDAID brand adhesive strips), or transdermal patches. Carriers such as cocoa butter, viscous polyethylene glycols, hydrogenated oils, and such mixtures can be emulsified if desired.

[0062] Compounds of the subject invention may also be incorporated into cosmetics. Additional materials and substances suitable as carriers for the compounds of formulas I-V are described in the International Cosmetic Ingredient Dictionary and

Handbook, 8th Edition (The Cosmetic, Toiletry, and Fragrance Association (CTFA), 2000), hereby incorporated by reference in its entirety.

[0063] Where the pharmaceutical compositions are aerosols, the active ingredients can be packaged in pressurized aerosol containers with a propellant, e.g., carbon dioxide, nitrogen, propane, etc. with the usual adjuvants such as cosolvents, wetting agents, etc.

[0064] In accordance with the invention, pharmaceutical compositions comprise, as an inactive ingredient, an effective amount of one or more non-toxic, pharmaceutically acceptable ingredient(s). Examples of such ingredients for use in the compositions include ethanol, dimethyl sulfoxide, glycerol, silica, alumina, starch, calcium carbonate, talc, flour, and equivalent non-toxic carriers and diluents.

[0065] The pharmaceutical compositions herein will contain, per dosage unit, e.g., tablet, capsule, powder injection, teaspoonful, suppository, bandage, and the like, from about 0.1 to about 400 mg of the active ingredient. In a preferred embodiment, the compositions comprise about 10mg to 200 mg per dosage unit. In an even more preferred embodiment, the compositions contain comprise about 20mg to about 100mg of active ingredient. In another embodiment, the compositions comprise about 25mg of active ingredient per unit dose.

[0066] Topiramate is currently available for oral administration in round tablets containing 25 mg, 100 mg or 200 mg of active agent. The tablets contain the following inactive ingredients: lactose hydrous, pregelatinized starch, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, purified water, carnauba wax, hydroxypropyl methyl cellulose, titanium dioxide, polyethylene glycol, synthetic iron oxide, and polysorbate 80.

[0067] It should be understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and the scope of the appended claims. All publications and patents cited herein are hereby incorporated by reference in their entireties.

Example 1- Effects of topiramate on impulsivity and cognitive functioning

[0068] There are no reports of topiramate being utilized in PWS for any behavior. Measurements of attention, concentration, and impulsivity were assessed by the Delay and Vigilance tasks of the Gordon Diagnostic System (GDS; Gordon, M.; McClure, F.D.; & Aylward, G.P. (1996) *Gordon Diagnostic System, Interpretive Guide* (Third Edition); Dewitt, N.Y.: Gordon Systems, Inc.), a mechanized evaluator of cognitive functions, including attention and concentration. The GDS was originally developed, and most commonly used, to measure aspects of Attention-Deficit/Hyperactivity Disorder (ADHD) (previously called Attention-Deficit Disorder). One of the important components of the Vigilance test is the ability of an individual to have sustained attention, and the Delay task in part measures the subjects' ability to concentrate and focus on hitting a button at appropriate time intervals and delay impulsive behavioral responses.

[0069] The Delay Task requires that the subject inhibit responding (pressing a button and then refraining from pressing the button again for at least 6 seconds) in order to earn points. The Delay Task measures the subject's ability to suppress and delay impulsive behavioral responses. While focusing and sustaining attention usually facilitate Delay Task performance, the Delay Task maximally draws on a subject's ability to inhibit impulsive responses. The Delay Task's total efficiency ratio (EF) is considered the best indicator (score ranges from 0 to 1) of the level of impulsivity with the lower the score (such as less than .5) indicating higher impulsivity and poor self-control. The Vigilance Task measures the subject's ability to focus attention on a task and to maintain this attention over a period of time without reinforcement. The correct responses (CR) of the Vigilance Task measures the level of alertness and is a measure of the subjects attentional processes.

[0070] JAS-002 (patient Number 2) had a baseline total efficiency ratio (ER) of 0.02, approximately 8 standard deviations below the normal range and well below the first percentile in regards to the Delay task. This falls markedly within the range of an "abnormal" performance as stated in the rating score manual provided by the manufacturer of the GDS. At visit 4, approximately 1 month after starting medication (at a dose of 100 mg/day), JAS-002 demonstrated dramatic improvement in ER (a value of 0.98), well within the normal range of performance. At 2 months (at a dose of 175 mg/day), JAS-002 continued with improvements in ER (a value of 0.85), within the normal range of performance.

Attention as evaluated by the Vigilance Task for JAS-002 showed essentially no change for CR from 39 at baseline to 38 (at a dose of 175 mg/day) at 2 months.

[0071] For patient Number 1 (MJG-001), a significant improvement has been noted. At baseline, MJG-001's ER for the Delay Task was at a value of 0.06 (approximately 7 standard deviations below the average ER) demonstrating a severe impairment of impulsivity. However, at the second testing session, MJG-001 showed moderate improvement with a Delay Task ER of 0.24. At visit 5, approximately 1.5 months after starting medication (at a dose of 75 mg/day), MJG-001 demonstrated a substantial improvement with an ER value of 0.46 and two weeks later (at a dose of 125 mg/day) had an ER value of 0.70. At 2 months after starting medication (at a dose of 150 mg/day), MJG-001 demonstrated a substantial improvement with an ER value of 0.50. The Vigilance Task for MJG-001 showed some variability up and down during the study and, after approximately 2 months, showed a mild decrease of CR from 43 to 41 (at a dose of 150 mg/day).

[0072] Patient Number 3 (GFV-003) has also shown a severe deficit in impulsivity and focusing; baseline ER was 0.02 (a value 8 standard deviations below the normal range). At visit 1, after one week at a low dose of topiramate (25 mg/day), GFV-003 had improved to an 0.09 ER and by week 4 (at a dose of 100 mg/day) to an ER of 0.19, and by 2 months (at a dose of 200 mg/day) the ER was at 0.10. The Vigilance Task for GFV-003 showed variability on topiramate and by the end of two months was essentially unchanged with a CR decreasing from 16 at baseline to 15 at 2 months.

[0073] Patient #4 (MCK-004) also showed abnormal performance on the Delay task (ER of 0.35). Within 1 week on low dose topiramate (25 mg/day) MCK-004 had improved to an ER of 0.51, by the 2nd week on 50 mg/day topiramate, the ER was 0.76, and continued improvement by the 3rd week on 75 mg/day with an ER of 0.65 and by two months at a dose of 150 mg/day, her ER continued to be improved at 0.64. The Vigilance Task for MCK-004 shows mild decrease from baseline CR of 38 to 34 (by the 8th week on 150 mg/day).

[0074] Thus, the use of topiramate for impulsivity, without negative effects on attention and concentration, is both novel and clinically applicable. Disorders with impulsivity and deficits in attention and concentration are difficult to manage for both the patient and their caregiver, especially in cases of dementia. Impulsivity and lack of

concentration can severely handicap day-to-day functioning in all age groups affected by these disorders. There are no reports in the literature of topiramate specifically used to treat impulsivity and/or deficits in attention and concentration.

Example 2- Effect of topiramate on pathologic skin picking (PSP)

[0075] There are no reports of topiramate being utilized in PWS for any behavior. Patient #3 (GFV-003) also has pathologic skin picking (PSP) in addition to food seeking behavior. Patient #3 has a chronic large lesion on his lower left arm. Within one week of topiramate (25 mg/day), he had decreased skin picking and showed healing of this lesion on his left arm. By the 4th week on topiramate (at 100 mg/day), the lesion on his lower left arm had completely healed over. The progression of wound healing is provided in Figures 9A-D and 12A-B.

[0076] Patient #1 (MJG-001) has pathologic skin picking (PSP) in addition to food seeking behavior. Unexpectedly and serendipitously, it was observed that several large lesions (where she skin picks) on her right arm, legs, and lips were clearing up quickly (within 5 days) after topiramate was initiated at 25 mg/day. Furthermore, the patient has continued to do well in terms of skin clearing. For example, a large lesion on her right arm completely healed over after about 2 months on topiramate (at a dose of 125 mg/day). The patient lives in a group home and workers there, as well as her mother, have also commented to us that her skin picking/skin has overall improved. The progression of wound healing is provided in Figures 10A-C and 11A-B.

[0077] The use of topiramate for PSP and related disorders is also novel and clinically applicable. There are no FDA approved pharmacological treatments for pathologic skin picking (also referred to as neurotic excoriation, repetitive skin picking, compulsive skin picking, and dermatotillomania) and possible related obsessive-compulsive spectrum disorders (*i.e.*, repetitive self-mutilation (RSM), oncophagia, rhinotillxomania, trichotillomania) (Goldsmith, T.D.; Shapira, N.A.; Phillips, K.A.; *et al.*, "Obsessive compulsive spectrum disorders"; in: Swinson, R.P.; Antony, M.M.; Rachman, S.; Richter, M.A. (Eds)., *Obsessive-Compulsive Disorder: Theory, Research, and Treatment*, Guilford Publications, New York, pp.397-425 (1998)).

Example 3 – Effects of Topiramate on patients with Prader-Willi Syndrome

[0078] In an 8-week, open-label, flexible-dose (maximum 350mg/day) study to evaluate the efficacy and safety of topiramate in PWS adults, weekly evaluations were performed that included scales for stereotypical behavior (Stereotypy Checklist, Y-BOCS checklist), aberrant behavior (Aberrant Behavior Scale {ABS}, Severity of Symptoms Scale, Self-Injury and Self-Restraint Checklist) and cognitive functioning (Gordon Diagnostic, Controlled Oral Word Association Test, Semantic Naming test). Subject safety measures were also performed (*e.g.*, monitoring blood pressure). Appetite was assessed for one hour at four time points during the trial. Measurements were made by investigator observation of the subject with free access to low calorie food and a visual analogue scale before and after observation.

[0079] Eight subjects (19-36 years of age; 4 males and 4 females) entered the trial and six have completed the treatment regimen. A mean weight loss of 0.3 pounds was observed over the course of the study. Appetite tests show a mean increase of 255.8 calories/hour; however, a dramatic reduction in self-injurious behavior was also observed (*e.g.*, skin picking). Five subjects have continued long-term on topiramate for at least 6 months (mean of 8.2 $\pm$ 1.5 months) and, in these subjects, there has been mean 4.9 lb $\pm$ 4.0 lb weight loss. Behavior evaluations have shown a reduction in aberrant behaviors (such as irritability and noncompliance [Mean ABS at baseline of 8.5 $\pm$ 7.2 and mean ABS at week 8 of 5.3 $\pm$ 5.1, *Z= -2.0, df=1, P= .042 {Wilcoxon signed-ranks test}]) and self-injury in all four subjects exhibiting these behaviors. Healing of skin lesions was also observed. Open-label administration of topiramate has been shown to improve behavior and decrease self-injury in PWS subjects. Longer treatment lengths appear to result in steady weight decrease.

Example 4 – Effects of Topiramate on Prader-Willi Syndrome

[0080] In the above study was performed to assess the effects of topiramate on PWS. All subjects provided written informed consent for topiramate treatment and were between 18 and 65 years of age. Criteria for exclusion included: clinically significant suicidality or homicidality; current or recent (within 6 months of the start of topiramate) DSM-IV diagnosis of substance abuse or dependence; a clinically unstable disease that could interfere with treatment or assessment of PWS; treatment with any drug that might interact adversely with topiramate; and personal or family history of nephrolithiasis. Women of

childbearing potential who were not taking adequate contraceptive measures were not included. Screening measures included a physical examination, psychiatric background, medication history, blood draw for laboratory assessment (CBC, SMA-12, urinalysis, and a B-hCG for women of childbearing potential), and the Structured Clinical Interview for DSM-IV, Patient Edition (SCID-P). Weekly assessments of weight loss, participant functioning, and safety measures including blood pressure and pulse were taken by the investigators at each visit. Participants are residents of group homes operated by the Association of Retarded Citizens, Alachua County, Florida (ARC). These homes are monitored, thereby allowing recording of participants' behavioral and psychiatric manifestations as well as their medication management. Participants began pharmacotherapy with topiramate at 25 mg of drug given in the evening for 7 days. After 14 days, their daily dose could be increased in increments of up to 50 mg/week for the next 6 weeks.

[0081] Case 1: Ms. A. is a 19 year-old female who through DNA methylation testing was positive for PWS and shown to have a chromosomal deletion through FISH and DNA polymorphism analyses. Ms. A. has a history of hoarding and severe skin picking dating to childhood. Current concomitant psychiatric medications include fluoxetine 60 mg/day and naltrexone 50 mg/day. Psychiatric intervention dated back to 1992 when the subject began therapy with clomipramine and fenfluramine, both of which were unsuccessful in managing her behavior and weight problem.

[0082] Initial side effects (of topiramate) experienced included mild sedation, word-finding difficulties, and unrelated lower back pain that resolved by Week 8. Ms. A's weight remained stable with a baseline of 129.5lbs and weight of 128.5lbs at Week 8. Ms. A had a long-standing primary lesion on her right forearm that measured approximately 4cm by 1cm and ulcerated at baseline. She experienced a reduction in skin picking with improvement to the lesions on her face, arm, and legs noted by Week 4 (75mg/day). To better follow the improvement in her skin, a photographic record of Ms. A's lesion on her forearm was begun demonstrating healing of this lesion by Week 8 of topiramate (150 mg/day). See Figures 10A-C and 11A-B.

[0083] Case 2: Mr. B. is a 29 year-old male confirmed to be a chromosomal deletion as described above. He has a history of severe food seeking and skin picking dating to childhood. Mr. B does not have a history of taking psychotropic medications and had

declined a previous recommendation to take fluoxetine. Initial healing of his primary lesion (a round 1.5cm diameter ulcerated lesion) was noted within one week of initiating topiramate treatment (25mg/day) at which point photographic records were started. Mr. B also experienced some increased irritability when topiramate was initiated. Irritability returned towards baseline by Week 8. Mr. B also experienced a decrease in his weight from 180.0 lbs at baseline to 176.8 lbs at Week 8. By Week 8 of topiramate (200mg/day), Mr. B. had experienced remission of his self-injurious behavior (SIB) with resultant healing and complete unulceration of his primary lesion (Figures 9A-D and 12A-B).

[0084] Case 3: Ms. C. is a 32 year-old female confirmed to be a chromosomal deletion. Concomitant psychotropic medications include fluoxetine 20mg/day. She has a history of food seeking and skin picking dating to childhood. Due to her employment, Ms. C. picks in multiple concealed locations (*e.g.*, her chest, breasts, and the top of her legs). Because of her secrecy regarding SIB, the staff members of her group home daily perform full body surveys. As a result of previous experience with Ms. A and Mr. B, photographic records of her lesions were started prior to initiation of topiramate (Figure 13).

[0085] After beginning topiramate, an attenuation of SIB behavior and number of ulcerated lesions (Figure 14) was noted within 1 week (25 mg/day) by photographs and by 2 weeks (50 mg/day) by her group home staff. Side effects included word-finding difficulty, mild confusion, sedation, and some mild tingling in her left heel. All side effects resolved by Week 5. On topiramate, Ms. C experienced an increased weight from 150lbs at baseline to 154.5lbs at Week 8. At Week 8, Ms. C. had continued attenuation of skin picking on a dose of 175mg/day (Figures 14 and 15). During participation, Ms. C. experienced a period of three weeks where she was without any SIB. However, reportedly as result of her picking at several insect bites, small ulcerated lesions appeared on her forearm and lower legs in Weeks 7 and 8.

[0086] These three cases further illustrate the beneficial effects of the anti-epileptic drug topiramate. Topiramate is able to attenuate self-injurious behavior in a patient population where SIB is common and difficult to manage and treat. All three subjects have longstanding histories of self-injury, and two subjects (Ms. A. and C.) had failed previous psychotropic medication interventions. Furthermore, all three PWS subjects have chosen to continue on topiramate after the 8-week trial (8 months for Ms. A., 7 months for Mr. B., and

4 months for Ms. C.) with continued improvement in self-injury. Improvement in self-injury was noted by both investigators and in systematic body evaluations by the group home in one subject (Ms. C.). Additionally, while individuals with PWS often pick surreptitiously and pick even when they describe having no urges, all three subjects reported decreased urges to pick while on topiramate.

[0087] In terms of an objective measurement of impulsivity, subjects were also followed by the Delay Task of the computerized Gordon Diagnostic System (Gordon *et al.*, 1996). The Delay Task measures a subject's ability to suppress and delay impulsive behavioral responses (Gordon *et al.*, 1996). All three subjects demonstrated improvement in the Delay Task while on topiramate.

Example 5 – Effects of Topiramate on Impulsive Disorders in Mammals

[0088] Canine acral lick dermatitis (ALD), also known as lick granuloma, acral pruritic nodule, and neurodermatitis, is a common self-inflicted skin disorder in dogs in which localized alopecia and epidermal hyperplasia and fibrosis are caused by continued licking, biting, and/or scratching one or more areas usually near the carpus or hock. When severe, the licking of the paws or flank causes significant local trauma and, in extreme cases, may require surgery and steroids. Occasionally, the animal must be put to death because of chronic ulceration or osteomyelitis. The etiology of ALD is unknown, although, commonly, it is considered to be psychogenic in origin secondary to boredom, loneliness, or confinement. It can also be provoked by local irritation. Certain large breeds appear to be more susceptible, such as German Shepherds, Labrador Retrievers, and Great Danes. The repetitive self-licking, chewing, or scratching creates areas of hair loss and the production of lesions which may range in size from several centimeters to the entire surface of the limb. This stereotypic behavior prevents the lesions from healing and may cause discomfort, pain and, in severe cases, may prove crippling.

[0089] Twenty dogs will be recruited from the Veterinary Animal Teaching Hospital. Other causes of licking will be ruled out by examining the dogs' clinical history, typical lesion appearance, and past history of treatment response. Dogs must exhibit chronic licking of 6 months or more that has caused an observable lesion(s). Reasons for exclusion from the study include: dogs undergoing concurrent treatment for ALD, dogs weighing <5 kg, dogs that have not been neutered or spayed, nephrolithiasis, and a significant acute or

chronic confounding disease. Once the referring veterinarian has consented to the dogs' involvement, letters inviting participation in the study will be sent out to the owners of appropriate candidates. An informed consent documents will also be obtained.

[0090] A double-blind placebo-controlled trial of 8 weeks duration (6 week treatment and 2 week taper) will be conducted. One-half of the dogs receive placebo. The dogs will start at 2 mg/kg in a split dose (1mg/kg twice a day) for the first two weeks. The dose will be increased 2 mg/kg a week as tolerated for the next four weeks. Thus, the maximum dosage will not exceed 10 mg/kg. This dosage strategy is based upon the target dose for seizures, which is 5 to 10 mg/kg in split doses.

[0091] Topiramate or placebo will be administered via gelatin capsules once daily (5 minutes before feeding). Owners will be instructed to avoid feeding dogs anything in addition to their regular diet. In addition to adhering to the dogs' routine (*e.g.*, food, exercise, and training), owners will also be asked to maintain environmental conditions for the duration of the study.

[0092] A video camera will record the dogs' behavior for 1 hour each week for the 6 weeks of the trial. The primary behavior of interest is self-licking or self-chewing of the granulomatous lesion. The measure of time the dogs are involved in licking or chewing will be computerized. The evaluator will press the designated key when the dog's tongue or lips first makes contact with the lesion, and at the end of a continuous bout of licking or chewing when the dog lifts its head from the lesion and transfers its attention elsewhere.

[0093] In addition to videotaping, the owners will rate their dogs' licking behavior on a 10-point scale, with 10 being the worst ever observed and 0 indicating a complete absence of excess licking (Acral Lick Dermatitis Severity Scale). Investigators will also rate the dogs' behavior using a similar scale. Finally, photographs of the lesions will be taken weekly. Additionally, at baseline, a checklist for phobias will be done with the owners and the list will be reviewed each week using clinical global impression scales to rate phobias.

[0094] A 2-week taper period will follow the 6-week treatment period. During week 7, study medication will be reduced by approximately 25% for 3 days. On day 4, the dosage will be reduced by another 25%. On day 11 the remaining dose will be reduced in

half again and on day 13 all study medication will be stopped. The dogs' last visit will be day 14 of the taper period.

[0095] For each of the efficacy measures, a listing of each patient's score at each study week during treatment will be generated. The evaluation of change in efficacy measurements will be carried out using standard analysis of variance techniques. All statistical tests will be two-sided if not otherwise specified. A test will be said to be significant if $p<0.05$. Analyses will be preformed using the "intent-to-treat" population consisting of all dogs randomized into the trial who take at least one capsule of study medication and had at least one post-baseline evaluation. The primary efficacy variable will be the number of self-injurious behaviors observed by video camera during weekly visits. A dog's self injury duration (in min/hr) is measured at the baseline and six weeks after treatment. The improvement score is the percentage of reduction (in ratio), *i.e.*, improvement = (baseline - posttreatment)/baseline.

Example 6- Effects of topiramate on trichotillomania

[0096] Topiramate was used as an adjunct therapy in a 38 year-old female with a 9-year history of trichotillomania. She was on a stable dose combination of fluvoxamine and clomipramine. While the fluvoxamine/clomipramine combination was therapeutic for 3 years, 6 months ago Ms. A experienced an increase in hair pulling predominately on the left side of her head. The investigators have made photographic records of Ms. A.'s hair loss (Figures 15A-B) and she has been evaluated psychometrically for impulse control. Ms. A was started on a 25mg dose of topiramate at night and was gradually titrated in increments of 25mg to 150mg at night. Preliminary results suggest the addition of topiramate to this combination therapy effective for trichotillomania.

[0097] Before topiramate was initiated, clomipramine blood levels were as follows: clomipramine = 354 ng/ml, DM clomipramine = 118ng/ml, and clomipramine + DM clomipramine = 472 ng/ml. Following the addition of topiramate Ms. A reported a lessening of the urges to pull her hair starting at a relatively low dose (approximately 50mg/ day). Ms. A reported a significant reduction in the urge to pull by 3 weeks following the addition of topiramate and this improvement has been maintained for 14 weeks (Figure 16). Although patient described decreased urges to pull hair, her re-growth was minimal. Subsequent laboratory assessments when patient was on 150 mg of topiramate, 100 mg of clomipramine

and 50 mg of fluvoxamine showed that although the ratio of parent to metabolite were the same as before topiramate (.69), both measurements were elevated: clomipramine = 514 ng/ml, DM clomipramine 181 ng/ml, clomipramine + DM clomipramine = 695 ng/ml.

[0098] After initial success with topiramate augmentation, the patient is currently being weaned off clomipramine and is currently on 25mg/day from 100mg/day without any increase in urges to hair pull. Ms. A has experienced weight loss of approximately 5 lbs which she reports as a positive side effect. Possible other side effects of topiramate administration include disruption of attention and concentration and cognitive deficits such as word finding difficulties.

[0099] Ms. A has been evaluated psychometrically for these side effects. Results from the Delay task of the Gordon Diagnostic System, a widely used measurement of impulse control, have shown improvements from baseline (Figure 17). Subsequent testing of word finding abilities through the Control Oral Word Association Test (COWAT) and Semantic Category Naming test have shown no significant changes from baseline (Figure 18).

[00100] The patient has continued to see a reduction in the urge to, as well as in the time spent, pull her hair. Re-growth of hair at the sites previously pulled has also been observed. The patient is currently on 475 mg topiramate (p.o. q.h.s.).

Example 7 – Effects of Topiramate on Trichotillomania

[0100] A 19 year old female with a history of trichotillomania and skin picking has also been treated in accordance with the invention. She presented with skin lesions on her hands and face that resulted from picking at pimples (face) and pulling of hair on the backs of her hands. Several medications, in various classes, were previously tried without improvement (including mirtazapine, citalopram, gabapentin, paroxetine, nefazadone, and sertaline). The initiation of topiramate has resulted in the resolution of her trichotillomania, with noticeable re-growth of hair on the backs of her hands at 200 mg. p.o. q.h.s.) and has also resulted in improvements in the facial skin lesions. She is currently on 300 mg q.d. topiramate monotherapy.

Claims

What is claimed is:

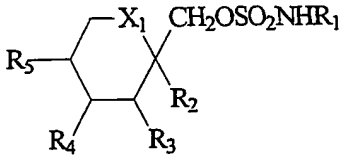
1. A method for treating or controlling neurogenetic disorders in an individual comprising the administration of a therapeutically effective amount of a composition comprising an anti-convulsant agent and a pharmaceutically acceptable carrier.

2. The method according to claim 1, wherein said neurogenetic disorder is compulsive buying, problematic Internet use, or an impulse control disorder selected from the group consisting of intermittent explosive disorder, kleptomania, pyromania, pathologic gambling, and trichotillomania.

3. The method according to claim 1, wherein said neurogenetic disorder is Prader-Willi Syndrome.

4. The method according to claim 1, wherein said neurogenetic disorder is attention deficit hyperactivity disorder.

5. The method according to claim 1, wherein said anti-convulsant agent is selected from the group consisting of:



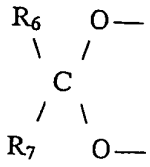
(Formula I)

wherein

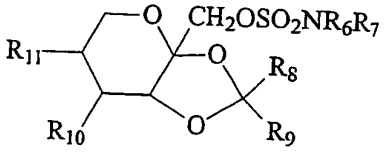
X_1 is CH_2 or oxygen;

R_1 is hydrogen or alkyl; and

R_2, R_3, R_4, and R_5 are independently hydrogen or lower alkyl and, R_2 and R_3 and/or R_4 and R_5 together may be a methylenedioxy group of the following formula:



wherein R_6 and R_7 are the same or different and are hydrogen, lower alkyl or are alkyl and are joined to form a cyclopentyl or cyclohexyl ring,

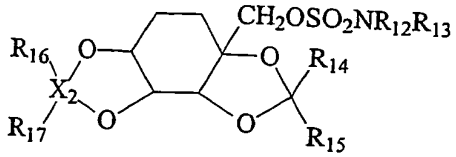


(Formula II)

wherein R_6 and R_7 may be the same or different and are hydrogen or C_1 to C_4 alkyl;

wherein R_8 and R_9 may be the same or different and are hydrogen or C_1 to C_4 alkyl;

wherein R_{10} and R_{11} may be the same or different and are azido, halogen, hydroxyl, sulfamoyl (H_2NSO_2O), C_1 to C_4 alkoxy, C_1 to C_4 alkyl thiocarbonate (RSC(O)O), C_1 to C_4 alkyl carbonate (ROC(O)O), or C_1 to C_4 alkyl carboxylate (RC(O)O), wherein R is C_1 to C_4 alkyl,

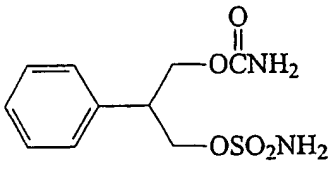


(Formula III)

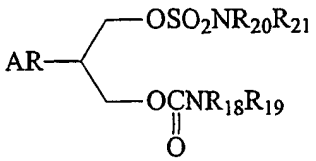
wherein R_{12} and R_{13} may be the same or different and are hydrogen, alkyl (C_1 to C_6), cycloalkyl (C_3-C_7), allyl, or benzyl;

R_{14} and R_{15} are the same or different and selected from hydrogen or lower alkyl; and

X_2 may be chosen from carbon (C) or sulfur (S), with the stipulation that when X_2 is carbon, R_{16} and R_{17} are the same or different and are selected from hydrogen or lower alkyl, whereas when X_2 is sulfur one of R_{16} and R_{17} is oxygen and the other is a lone pair of electrons or both R_{16} and R_{17} are oxygen,

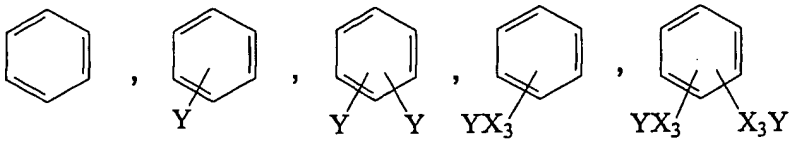


(Formula IV), and



(Formula V)

wherein, AR is represented by the following formulas;



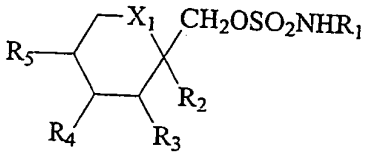
Y is selected from the group consisting of halogens, trifluoromethyl and alkyl groups containing 1 to 3 carbon atoms when Y alone is attached to the benzene ring; or

when X_3, which may be S or O, is present, Y is selected from the group consisting of trifluoromethyl and alkyl groups containing 1 to 3 carbon atoms; and

R_{18}, R_{19}, R_{20}, and R_{21}, may be identical or different and are selected from the group consisting of hydrogen, linear or branched alkyl groups containing 1 to 16 carbon atoms, cyclic alkyl groups containing 3 to 16 carbon atoms and aryl groups containing 6 to 8 carbon atoms, and $NR_{18}R_{19}$ and $NR_{20}R_{21}$, which may be identical or different, each may form a 3 to 7-membered aliphatic cyclic compound together with another nitrogen atom or oxygen atom.

6. A method for promoting wound healing comprising the administration of a therapeutically effective amount of a composition comprising an anti-convulsant agent and a carrier.

7. The method according to claim 6, wherein said anti-convulsant agent is selected from the group consisting of:



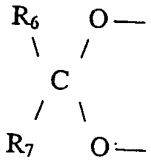
(Formula I)

wherein

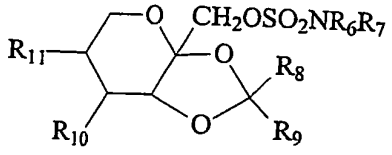
X_1 is CH_2 or oxygen;

R_1 is hydrogen or alkyl; and

R_2, R_3, R_4, and R_5 are independently hydrogen or lower alkyl and, R_2 and R_3 and/or R_4 and R_5 together may be a methylenedioxy group of the following formula:



wherein R_6 and R_7 are the same or different and are hydrogen, lower alkyl or are alkyl and are joined to form a cyclopentyl or cyclohexyl ring,

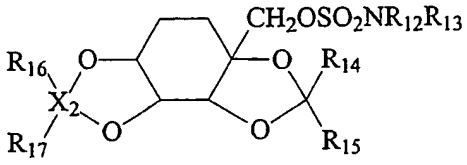


(Formula II)

wherein R_6 and R_7 may be the same or different and are hydrogen or C_1 to C_4 alkyl;

wherein R_8 and R_9 may be the same or different and are hydrogen or C_1 to C_4 alkyl;

wherein R_{10} and R_{11} may be the same or different and are azido, halogen, hydroxyl, sulfamoyl (H_2NSO_2O), C_1 to C_4 alkoxy, C_1 to C_4 alkyl thiocarbonate (RSC(O)O), C_1 to C_4 alkyl carbonate (ROC(O)O), or C_1 to C_4 alkyl carboxylate (RC(O)O), wherein R is C_1 to C_4 alkyl,

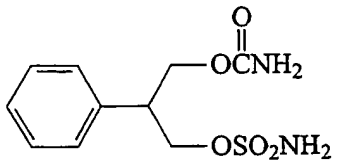


(Formula III)

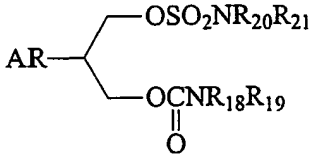
wherein R_{12} and R_{13} may be the same or different and are hydrogen, alkyl (C_1 to C_6), cycloalkyl (C_3-C_7), allyl, or benzyl;

R_{14} and R_{15} are the same or different and selected from hydrogen or lower alkyl; and

X_2 may be chosen from carbon (C) or sulfur (S), with the stipulation that when X_2 is carbon, R_{16} and R_{17} are the same or different and are selected from hydrogen or lower alkyl, whereas when X_2 is sulfur one of R_{16} and R_{17} is oxygen and the other is a lone pair of electrons or both R_{16} and R_{17} are oxygen,

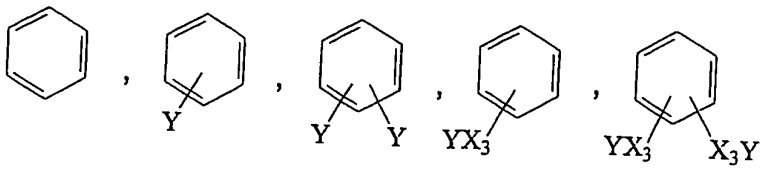


(Formula IV), and



(Formula V)

wherein, AR is represented by the following formulas;



Y is selected from the group consisting of halogens, trifluoromethyl and alkyl groups containing 1 to 3 carbon atoms when Y alone is attached to the benzene ring; or

when X_3, which may be S or O, is present, Y is selected from the group consisting of trifluoromethyl and alkyl groups containing 1 to 3 carbon atoms; and

R_{18}, R_{19}, R_{20}, and R_{21}, may be identical or different and are selected from the group consisting of hydrogen, linear or branched alkyl groups containing 1 to 16 carbon atoms, cyclic alkyl groups containing 3 to 16 carbon atoms and aryl groups containing 6 to 8 carbon atoms, and $NR_{18}R_{19}$ and $NR_{20}R_{21}$, which may be identical or different, each may form a 3 to 7-membered aliphatic cyclic compound together with another nitrogen atom or oxygen atom.

8. The method according to claim 6, wherein said composition comprises a salve, ointment, aerosol, cosmetic, or bioadhesive.

9. The method according to claim 6, wherein said composition is administered as a component of a bandage, transdermal patch, wound dressing, cosmetic, or bioadhesive.

10. The method according to claim 8, wherein said composition is a component of a bandage, wound covering, or wound dressing.

11. The method according to claim 1, wherein the therapeutically effective amount is about 0.1 to 400 mg.

12. The method according to claim 1, wherein the therapeutically effective amount is about 10 to 200 mg.

13. The method according to claim 1, wherein the therapeutically effective amount is about 25 mg.

14. The method according to claim 5, wherein the therapeutically effective amount is about 0.1 to 400 mg.

15. The method according to claim 5, wherein the therapeutically effective amount is about 10 to 200 mg.

16. The method according to claim 5, wherein the therapeutically effective amount is about 25 mg.

17. The method according to claim 1, wherein said neurogenic disorder is pathological skin picking and related disorders.

18. The method according to claim 1, wherein said neurological disorders are self-injury, gouging, nail biting, explosive outbursts, oppositional behavior, or obsessive ruminations.

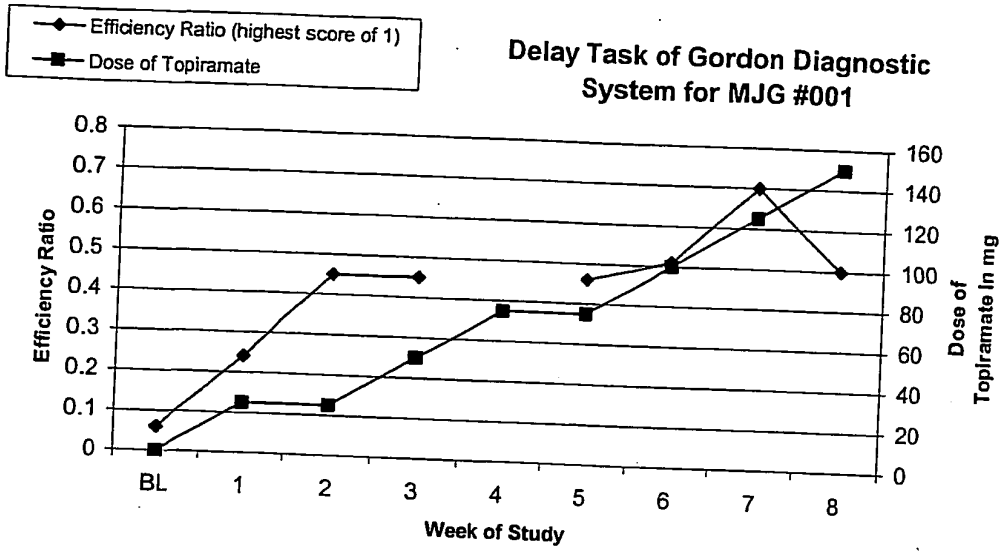

Efficiency Ratio (highest score of 1)
Dose of Topiramate
Delay Task of Gordon Diagnostic System for MJG #001
Efficiency Ratio
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
160
140
120
100
80
60
40
20
0
Dose of Topiramate In mg
BL
1
2
3
4
5
6
7
8
Week of Study

FIG. 1

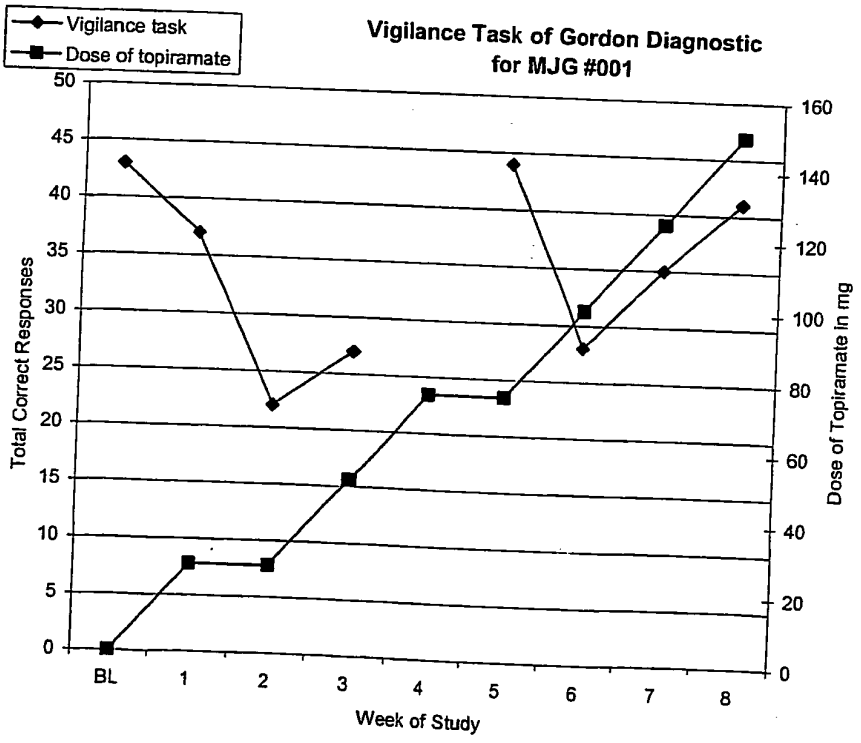

Vigilance task
Dose of topiramate
Vigilance Task of Gordon Diagnostic for MJG #001
Total Correct Responses
50
45
40
35
30
25
20
15
10
5
0
160
140
120
100
80
60
40
20
0
Dose of Topiramate In mg
BL
1
2
3
4
5
6
7
8
Week of Study

FIG. 2

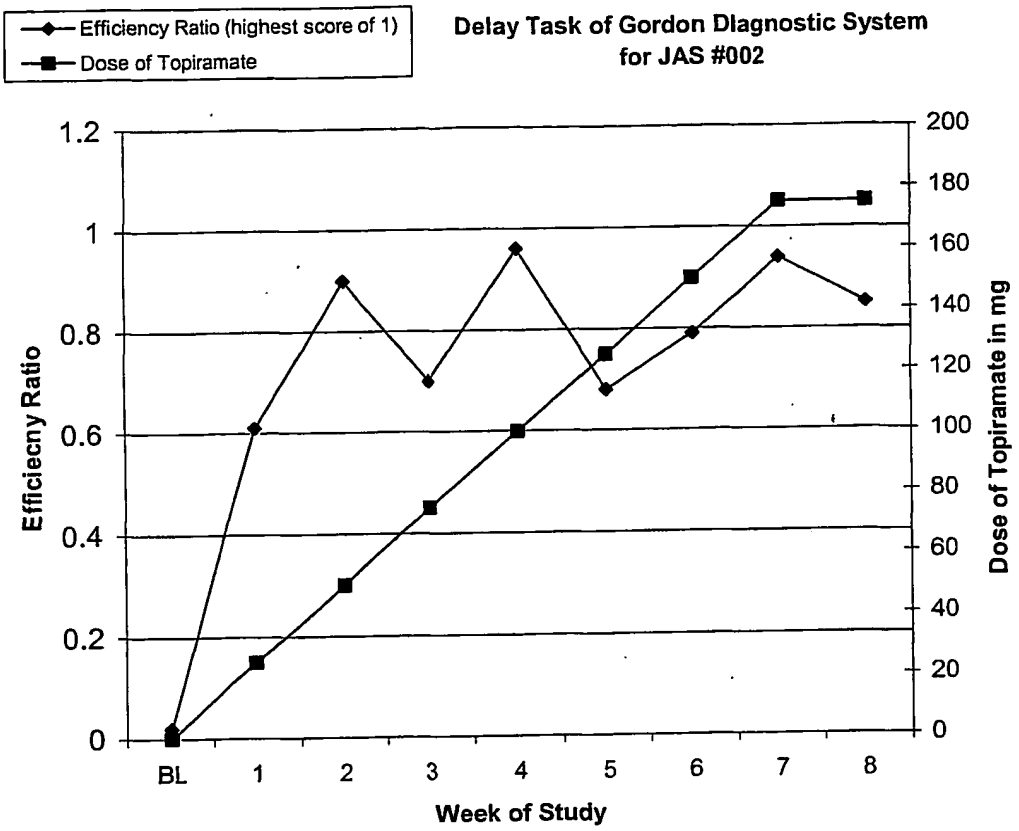

Efficiency Ratio (highest score of 1)
Dose of Topiramate
Delay Task of Gordon Diagnostic System for JAS #002
Efficiecny Ratio
Dose of Topiramate in mg
Week of Study
BL
1
2
3
4
5
6
7
8
0
0.2
0.4
0.6
0.8
1
1.2
0
20
40
60
80
100
120
140
160
180
200

FIG. 3

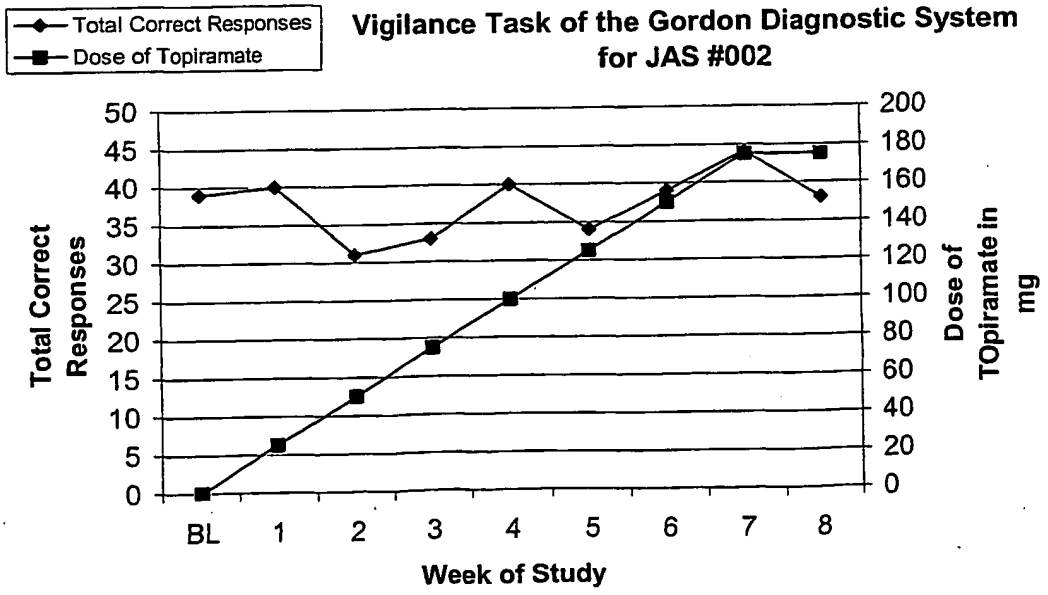

Total Correct Responses
Dose of Topiramate
Vigilance Task of the Gordon Diagnostic System for JAS #002
Total Correct Responses
Dose of TOpiramate in mg
Week of Study
BL
1
2
3
4
5
6
7
8
0
5
10
15
20
25
30
35
40
45
50
0
20
40
60
80
100
120
140
160
180
200

FIG. 4

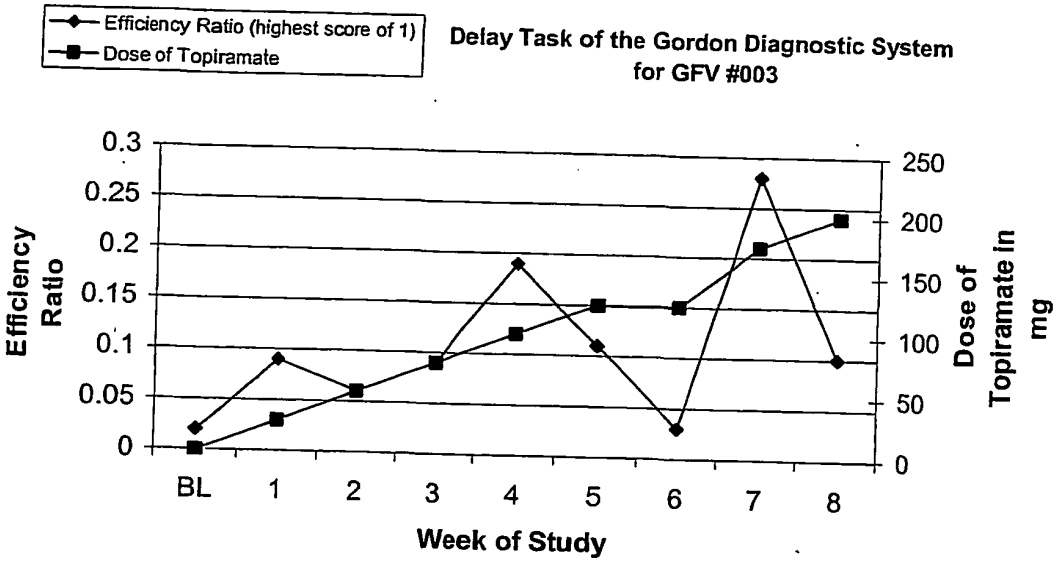

Efficiency Ratio (highest score of 1)
Dose of Topiramate
Delay Task of the Gordon Diagnostic System for GFV #003
Efficiency Ratio
0.3
0.25
0.2
0.15
0.1
0.05
0
250
200
150
100
50
0
Dose of Topiramate in mg
BL
1
2
3
4
5
6
7
8
Week of Study

FIG. 5

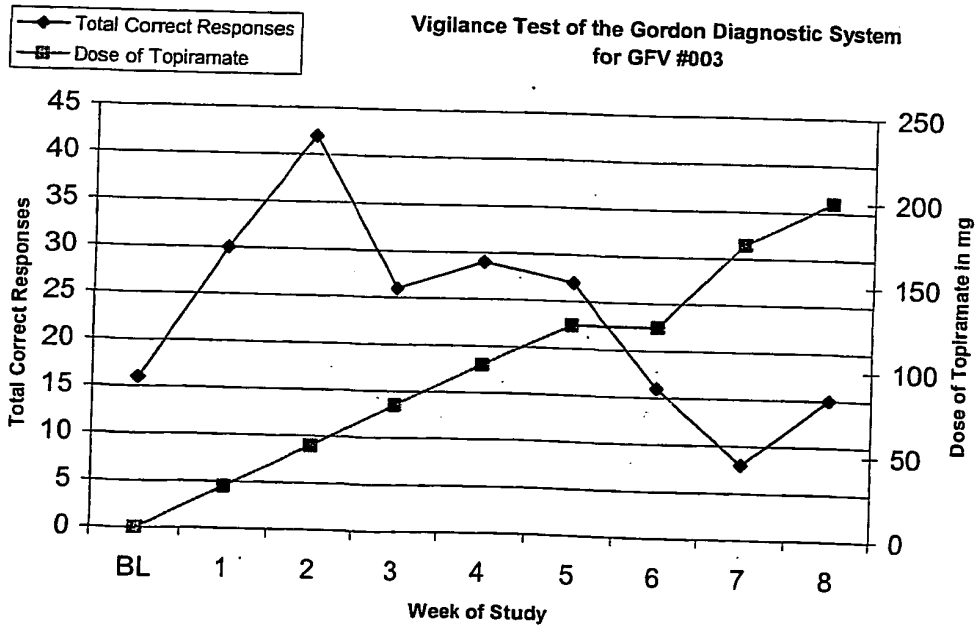

Total Correct Responses
Dose of Topiramate
Vigilance Test of the Gordon Diagnostic System for GFV #003
Total Correct Responses
45
40
35
30
25
20
15
10
5
0
250
200
150
100
50
0
Dose of Topiramate in mg
BL
1
2
3
4
5
6
7
8
Week of Study

FIG. 6

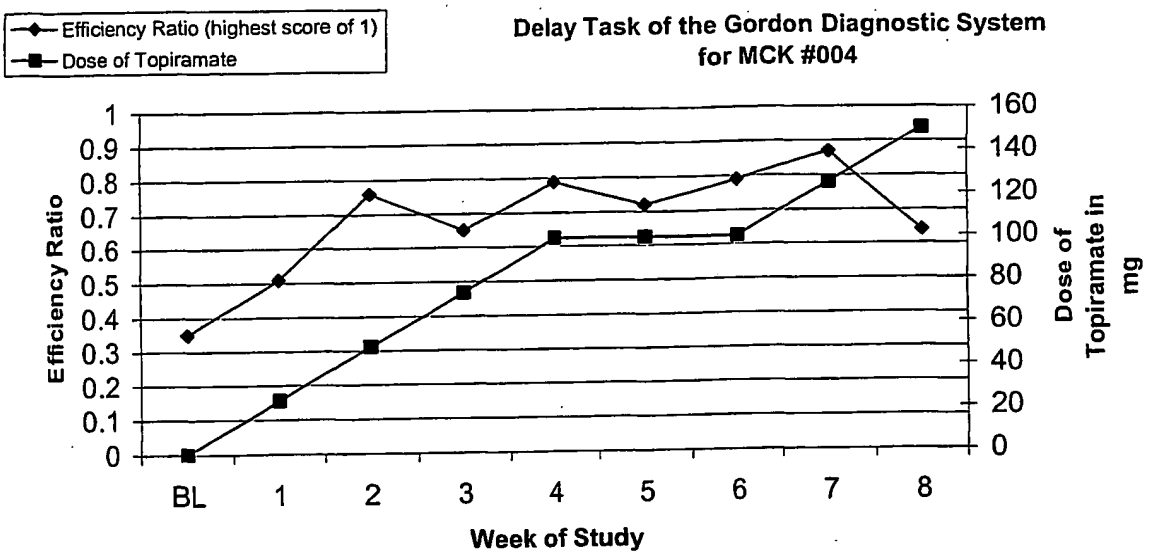

Efficiency Ratio (highest score of 1)
Dose of Topiramate
Delay Task of the Gordon Diagnostic System for MCK #004
Efficiency Ratio
Dose of Topiramate in mg
Week of Study
BL
1
2
3
4
5
6
7
8

FIG. 7

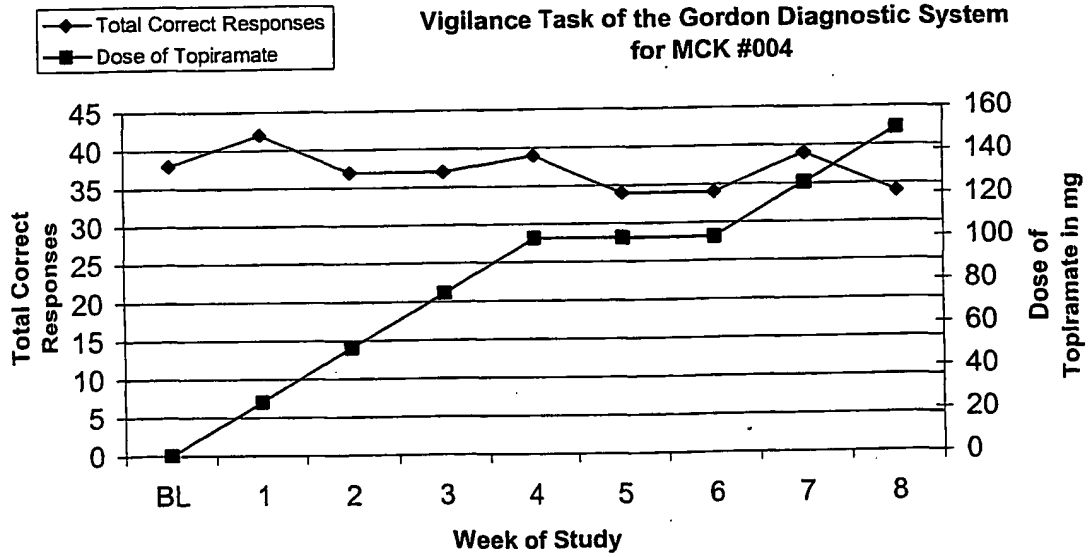
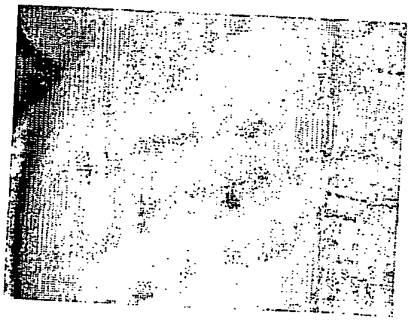

Total Correct Responses
Dose of Topiramate
Vigilance Task of the Gordon Diagnostic System for MCK #004
Total Correct Responses
Dose of Topiramate in mg
Week of Study
BL
1
2
3
4
5
6
7
8

FIG. 8

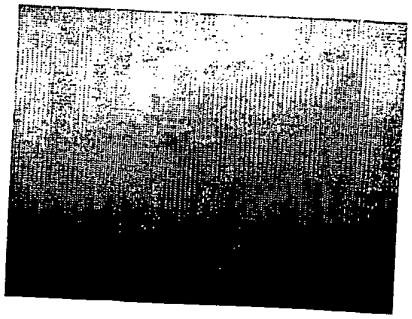
GFV-003
October 30, 2000
25 mg
Patient already showing healing on left arm lesion from decreased skin picking on low dose topiramate for 1 week. This lesion had been wet and oozing 1 week prior.

FIG. 9A



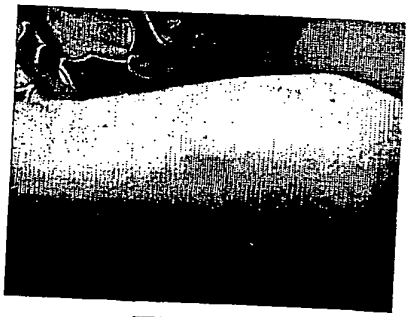
GFV-003
November 6, 2000
50 mg
Patient continues showing healing on left arm lesion from decreased skin picking.

FIG. 9B



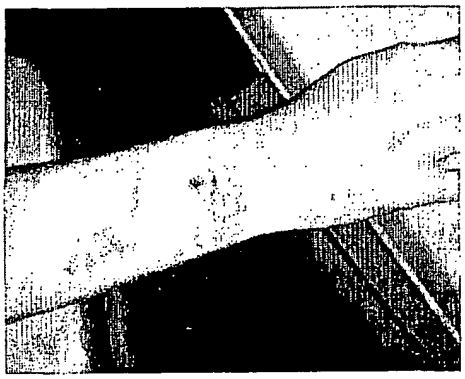
GFV-003
November 15, 2000
75 mg
Patient continuing to show healing on left arm lesion from decreased skin picking on topiramate as ths close up to the lesion shows.

FIG. 9C



GFV-003
November 21, 2000
100 mg
Patient with completely healed over lesion on left arm from decreased skin picking on topiramate.

FIG. 9D



MJG-001
October 27, 2000
75 mg
Patient's right arm skin lesion which had been completely open and wet approximately1 ½ months earlier shows healing with her decreased skin picking on topiramate

FIG. 10A

MJG-001
November 15, 2000
125 mg
Patient's skin is continuing to heal with decreased skin picking on topiramate.

FIG. 10B

MJG-001
November 20, 2000
125 mg
Patient's skin is showing significant healing with decreased skin picking on topiramate for approximately 2 months.

FIG. 10C

FIG. 11A

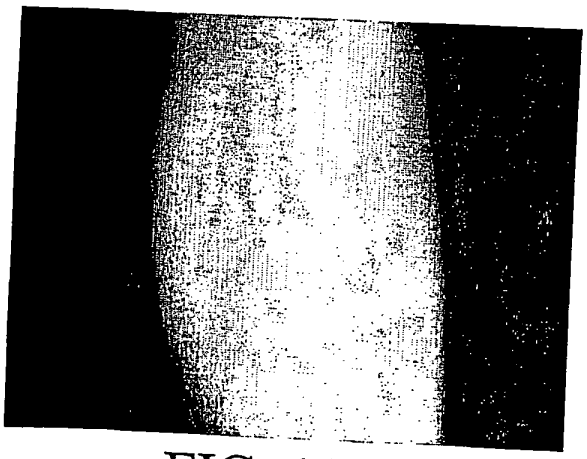


FIG. 11B

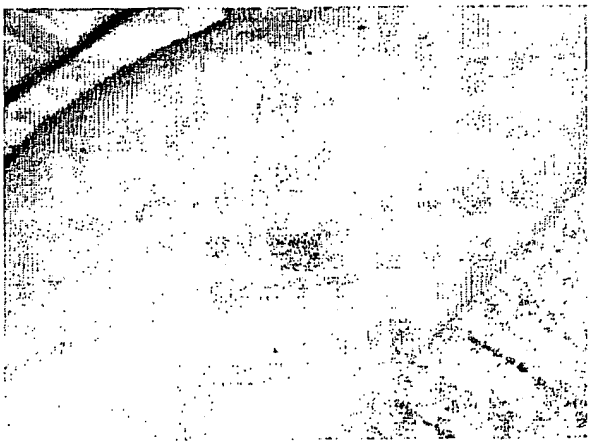


FIG. 12A

FIG. 12B

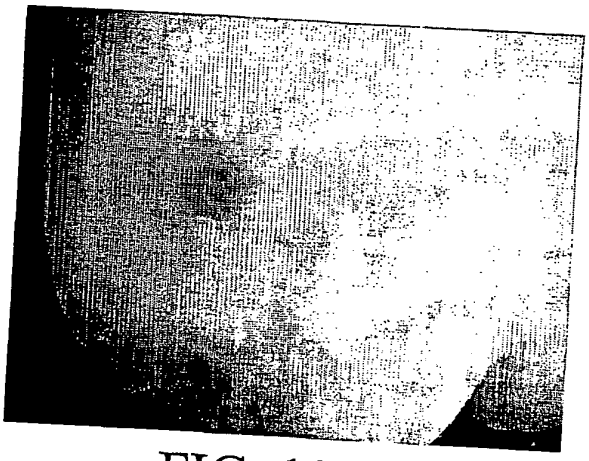


FIG. 13A

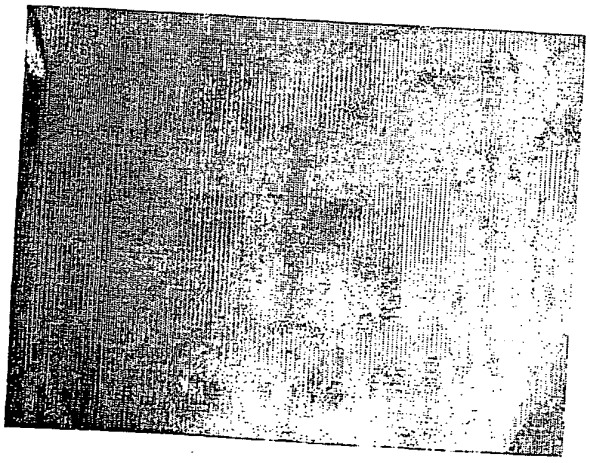
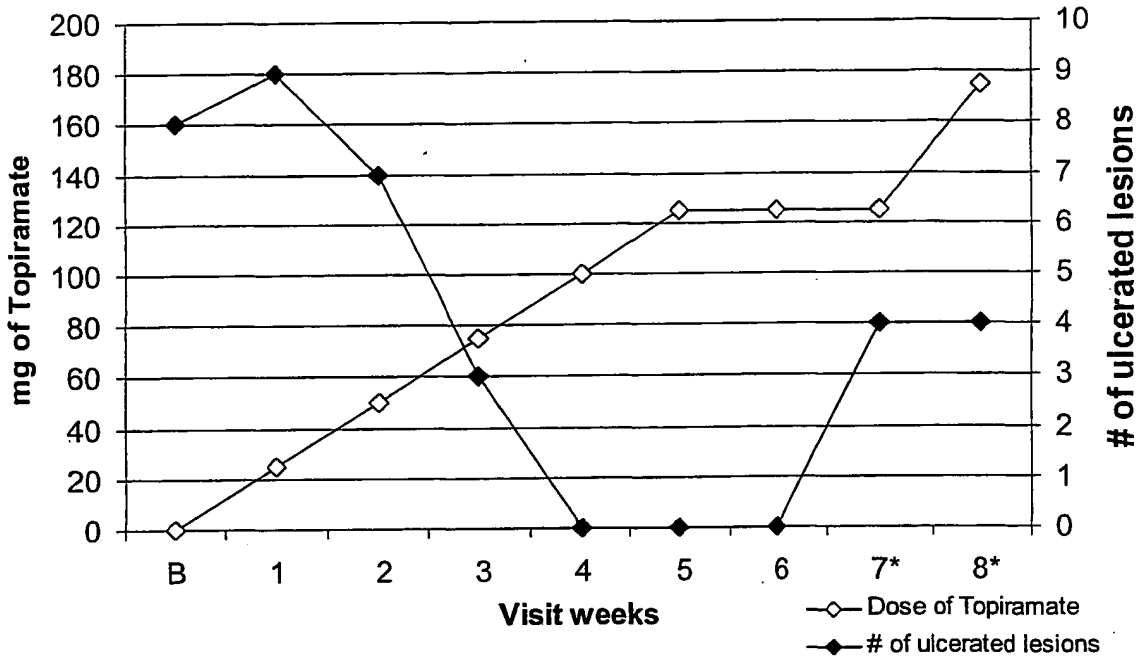


FIG. 13B



* lesions smaller than previous ones and appeared to result after insect bites

FIG. 14

FIG. 15A

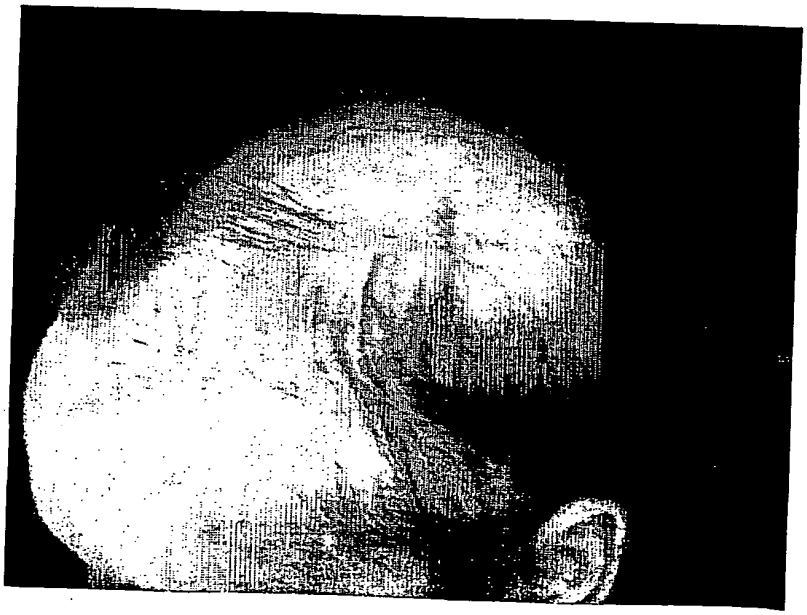


FIG. 15B

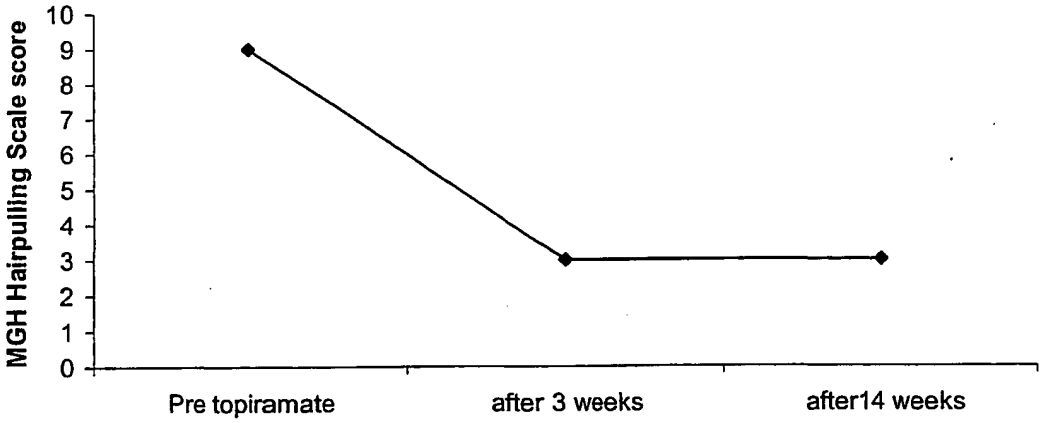


FIG. 16

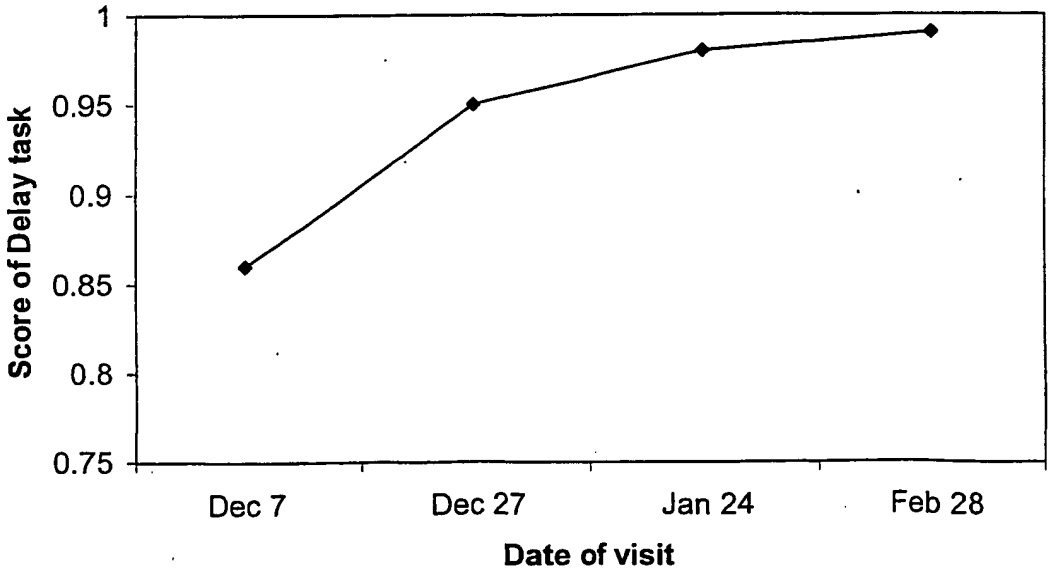


FIG. 17

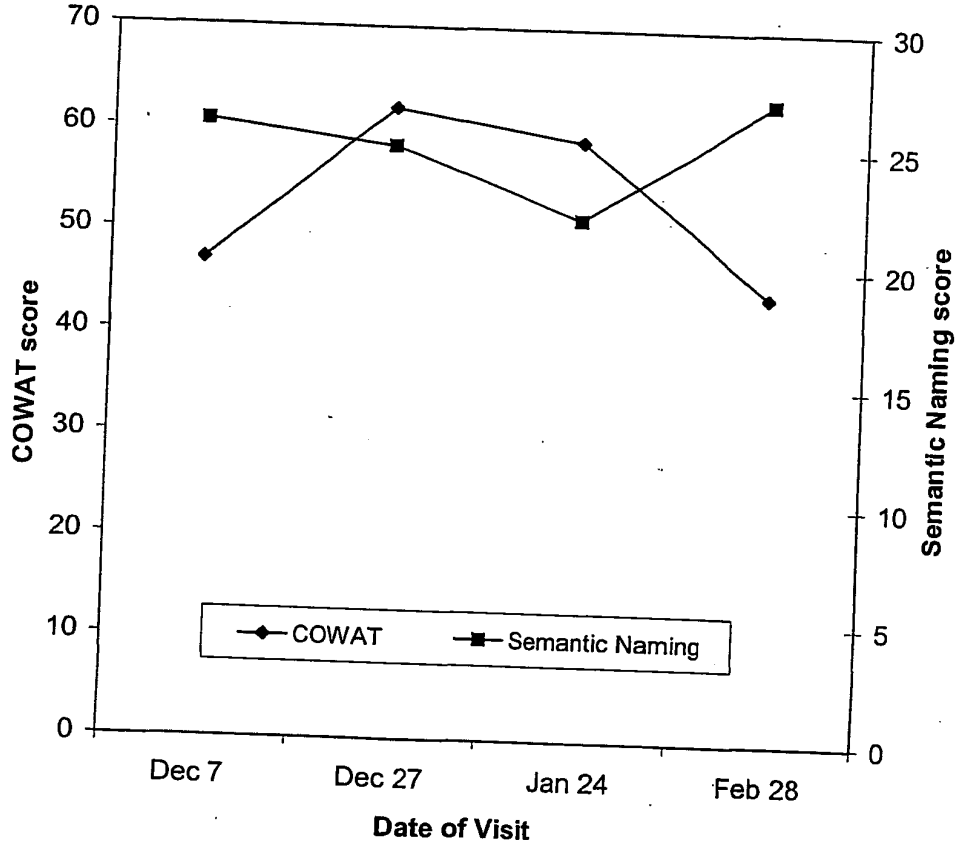

70
60
50
40
30
20
10
0
COWAT score
30
25
20
15
10
5
0
Semantic Naming score
COWAT
Semantic Naming
Dec 7
Dec 27
Jan 24
Feb 28
Date of Visit

FIG. 18

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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6 June 2002 (06.06.2002)

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(10) International Publication Number
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60/250,113 30 November 2000 (30.11.2000) US

(71) Applicant *(for all designated States except US)*: **UNIVERSITY OF FLORIDA** [US/US]; 223 Grinter Hall, Gainesville, FL 32611 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **SHAPIRA, Nathan, Andrew** [US/US]; 9520 SW 38th Lane, Gainesville, FL 32608 (US). **LESSIG, Mary, Catherine** [US/US]; 305 NE Sixth Avenue, Gainesville, FL 32601 (US). **DRISCOLL, Daniel, John** [US/US]; 8724 SW 46th Lane, Gainesville, FL 32608 (US).

(74) Agents: **EISENSCHENK, Frank, C.** et al.; Saliwanchik, Lloyd & Saliwanchik, A Professional Association, 2421 N.W. 41st Street, Suite A-1, Gainesville, FL 32606-6669 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report:
20 February 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/043731 A3

(54) Title: TREATMENTS FOR NEUROGENETIC DISORDERS, IMPULSE CONTROL DISORDERS, AND WOUND HEALING

(57) Abstract: The subject invention provides methods and compositions for the treatment of neurogenetic disorders, particularly DSM-IV impulse control disorders such as intermittent explosive disorder, kleptomania, pyromania, pathologic gambling, trichotillomania, and other impulse control disorders such as compulsive buying and problematic Internet use. In a preferred embodiment, the subject invention provides methods for treating or controlling symptons associated with ADHD or PWS comprising the administration of therapeutically effective amounts of compositions containing compounds of the formulas I-V. In another embodiment, the subject invention provides for methods of promoting wound healing comprising the administration of a therapeutically effective amount of a composition comprising the compounds of formulas I-V. Compositions may administered to a wound site via a salve, ointment, or as a component of a bandage or bioadhesive applied to the site of injury. The invention also provides therapeutically effective compositions comprising one or more of the compounds of formulas I-V.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/44923

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/35 A61K31/18 A61P25/00 A61P17/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 50020 A (MCELROY SUSAN L ;UNIV CINCINNATI (US)) 31 August 2000 (2000-08-31)	1-5, 11-18
A	page 2, line 20 -page 28, line 11; claims 1-14; tables 1,2	6-10
A	WO 98 15270 A (ORTHO PHARMA CORP) 16 April 1998 (1998-04-16)	1-5, 11-18
A	claims 1-4	6-10
A	WO 00 48549 A (ORTHO MCNEIL PHARM INC) 24 August 2000 (2000-08-24)	1-5, 11-18
A	page 3 -page 8; claims 1-10	6-10
A	WO 98 00131 A (ORTHO PHARMA CORP) 8 January 1998 (1998-01-08)	1-5, 11-18
A	claims 1-4	6-10

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 September 2002	24

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Kling, I

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00 23059 A (ORTHO MCNEIL PHARM INC) 27 April 2000 (2000-04-27) claims 1-4	1-5, 11-18 6-10
A	WO 00 28945 A (KAMMEN DANIEL P VAN ;ORTHO MCNEIL PHARM INC (US)) 25 May 2000 (2000-05-25) claims 1-4	1-5, 11-18 6-10
P,A	WO 00 76493 A (NAJARIAN THOMAS) 21 December 2000 (2000-12-21) claims 1-18	1-5, 11-18
A	WO 98 00129 A (ORTHO PHARMA CORP) 8 January 1998 (1998-01-08) page 2, line 15 -page 8, line 25; claims 1-4	1-5, 11-18 6-10

3

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/44923

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-18 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [X] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[X] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-5, 11-18

A method for treating or controlling neurogenetic disorders in an individual comprising the administration of a therapeutically effective amount of a composition comprising an anti-convulsant agent and a pharmaceutically acceptable carrier.

2. Claims: 6-10

A method for promoting wound healing comprising the administration of a therapeutically effective amount of a composition comprising an anti-convulsant agent and a carrier.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 01/44923

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 0050020 A	31-08-2000	AU	3599400 A	14-09-2000
		BR	0008477 A	22-01-2002
		CN	1360500 T	24-07-2002
		CZ	20013061 A3	12-06-2002
		EP	1158973 A2	05-12-2001
		NO	20014104 A	16-10-2001
		NZ	513643 A	28-09-2001
		WO	0050020 A2	31-08-2000
		US	2001023254 A1	20-09-2001
WO 9815270 A	16-04-1998	AU	725570 B2	12-10-2000
		AU	3602297 A	05-05-1998
		BR	9712503 A	19-10-1999
		CN	1232393 A	20-10-1999
		CZ	9901157 A3	15-09-1999
		EP	0932400 A1	04-08-1999
		HU	9904294 A2	28-04-2001
		JP	2001501643 T	06-02-2001
		NO	991621 A	25-05-1999
		NZ	334981 A	25-08-2000
		RU	2175868 C2	20-11-2001
		SK	45499 A3	14-08-2000
		WO	9815270 A1	16-04-1998
WO 0048549 A	24-08-2000	AU	3364800 A	04-09-2000
		CZ	20013011 A3	12-06-2002
		EP	1158950 A1	05-12-2001
		NO	20014026 A	17-10-2001
		NZ	513724 A	28-09-2001
		WO	0048549 A2	24-08-2000
		US	6214867 B1	10-04-2001
WO 9800131 A	08-01-1998	AT	214274 T	15-03-2002
		AU	725093 B2	05-10-2000
		AU	3501097 A	21-01-1998
		BR	9710993 A	26-02-2002
		CA	2258892 A1	08-01-1998
		CZ	9804279 A3	11-08-1999
		DE	69711067 D1	18-04-2002
		DK	936908 T3	27-05-2002
		EP	0936908 A1	25-08-1999
		HU	9904318 A2	28-05-2000
		JP	2000514426 T	31-10-2000
		NO	986054 A	01-03-1999
		NZ	333588 A	28-07-2000
		SK	180698 A3	11-07-2000
		WO	9800131 A1	08-01-1998
		US	5753694 A	19-05-1998
		ZA	9705764 A	28-12-1998
WO 0023059 A	27-04-2000	AU	1313100 A	08-05-2000
		BR	9914722 A	10-07-2001
		NO	20011901 A	18-04-2001
		WO	0023059 A2	27-04-2000
WO 0028945 A	25-05-2000	AU	6393399 A	05-06-2000
		BR	9915434 A	04-12-2001
		CN	1326346 T	12-12-2001

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 01/44923

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0028945 A		EP 1143917 A2	17-10-2001
		NO 20012423 A	16-05-2001
		WO 0028945 A2	25-05-2000
WO 0076493 A	21-12-2000	AU 5489600 A	02-01-2001
		EP 1187603 A1	20-03-2002
		WO 0076493 A1	21-12-2000
WO 9800129 A	08-01-1998	AT 204167 T	15-09-2001
		AU 730868 B2	15-03-2001
		AU 3957797 A	21-01-1998
		BR 9710992 A	24-10-2000
		CA 2258891 A1	08-01-1998
		CZ 9804276 A3	11-08-1999
		DE 69706195 D1	20-09-2001
		DE 69706195 T2	02-05-2002
		DK 964681 T3	08-10-2001
		EP 0964681 A2	22-12-1999
		ES 2160969 T3	16-11-2001
		JP 2000514796 T	07-11-2000
		NO 986053 A	23-02-1999
		NZ 333587 A	28-07-2000
		PT 964681 T	30-11-2001
		SI 964681 T1	30-04-2002
		SK 180398 A3	18-01-2000
		WO 9800129 A2	08-01-1998
		ZA 9705770 A	28-12-1998

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
6 June 2002 (06.06.2002)

PCT

(10) International Publication Number
WO 02/043731 A3

(51) International Patent Classification[7]: A61K 31/35, 31/18, A61P 25/00, 17/02

(21) International Application Number: PCT/US01/44923

(22) International Filing Date:
30 November 2001 (30.11.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/250,113 30 November 2000 (30.11.2000) US

(71) Applicant *(for all designated States except US)*: **UNIVERSITY OF FLORIDA** [US/US]; 223 Grinter Hall, Gainesville, FL 32611 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **SHAPIRA, Nathan, Andrew** [US/US]; 9520 SW 38th Lane, Gainesville, FL 32608 (US). **LESSIG, Mary, Catherine** [US/US]; 305 NE Sixth Avenue, Gainesville, FL 32601 (US). **DRISCOLL, Daniel, John** [US/US]; 8724 SW 46th Lane, Gainesville, FL 32608 (US).

(74) Agents: **EISENSCHENK, Frank, C.** et al.; Saliwanchik, Lloyd & Saliwanchik, A Professional Association, 2421 N.W. 41st Street, Suite A-1, Gainesville, FL 32606-6669 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *with amended claims*

(88) Date of publication of the international search report:
20 February 2003

Date of publication of the amended claims: 3 April 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/043731 A3

(54) Title: TREATMENTS FOR NEUROGENETIC DISORDERS, IMPULSE CONTROL DISORDERS, AND WOUND HEALING

(57) Abstract: The subject invention provides methods and compositions for the treatment of neurogenetic disorders, particularly DSM-IV impulse control disorders such as intermittent explosive disorder, kleptomania, pyromania, pathologic gambling, trichotillomania, and other impulse control disorders such as compulsive buying and problematic Internet use. In a preferred embodiment, the subject invention provides methods for treating or controlling symptons associated with ADHD or PWS comprising the administration of therapeutically effective amounts of compositions containing compounds of the formulas I-V. In another embodiment, the subject invention provides for methods of promoting wound healing comprising the administration of a therapeutically effective amount of a composition comprising the compounds of formulas I-V. Compositions may administered to a wound site via a salve, ointment, or as a component of a bandage or bioadhesive applied to the site of injury. The invention also provides therapeutically effective compositions comprising one or more of the compounds of formulas I-V.

AMENDED CLAIMS

[received by the International Bureau on 12 November 2002 (12.11.02); original claims 1, 2 and 4 amended; original claims 3 and 5-16 unchanged; original claims 17-18 cancelled (7 pages)]

What is claimed is:

1. A method for treating or controlling neurogenetic disorders in an individual comprising the administration of a therapeutically effective amount of a composition comprising an anti-convulsant agent and a pharmaceutically acceptable carrier;

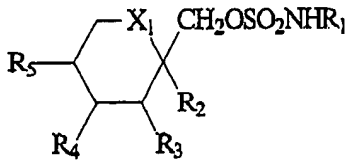
wherein said neurogenetic disorders are selected from the group consisting of hereditary ataxias and related disorders, Friedreich ataxia, ataxia telangiectasia, olivopontine cerebellar degeneration, Ramsay Hunt syndrome, abetalipoproteinemia, Machado-Joseph disease, familial spastic paraparesis, movement disorders, juvenile Huntington disease, dystonias, blepharospasm, spasmodic torticolis, tremor, myoclonus, Hallervorden-Spatz disease, phakomatoses, neurocutaneous syndromes, neurofibromatosis, tuberous sclerosis, Sturge-Weber, Von Hippel-Landau disease, mitochondrial encephalomyopathies, MELAS syndrome, Kearns-Sayre, Leigh disease, hereditary disorders of nerve and muscle, infantile spinal muscular atrophy, Charcot-Marie-Tooth disease, hereditary sensory and autonomic neuropathies, genetic myasthenic syndromes, metabolic myopathies, muscular dystrophies, myotonias, Laurence-Moon-Bardet-Biedl syndrome, Aicardi, Sjogren-Larsson syndrome, Prader-Willi syndrome, Angelman syndrome, gouging, oppositional behavior, and obsessive ruminations.

2. The method according to claim 1, wherein said neurogentic disorder is oppositional behavior.

3. The method according to claim 1, wherein said neurogenetic disorder is Prader-Willi syndrome.

4. The method according to claim 1, wherein said neurogenetic disorder is obsessive ruminations.

5. The method according to claim 1, wherein said anti-convulsant agent is selected from the group consisting of:



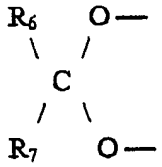
(Formula I)

wherein

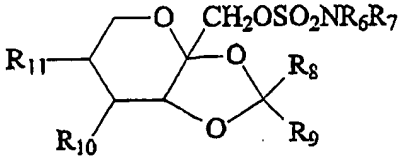
X_1 is CH_2 or oxygen;

R_1 is hydrogen or alkyl; and

R_2, R_3, R_4, and R_5 are independently hydrogen or lower alkyl and, R_2 and R_3 and/or R_4 and R_5 together may be a methylenedioxy group of the following formula:



wherein R_6 and R_7 are the same or different and are hydrogen, lower alkyl or are alkyl and are joined to form a cyclopentyl or cyclohexyl ring,

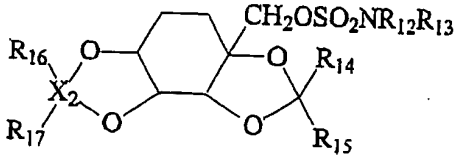


(Formula II)

wherein R_6 and R_7 may be the same or different and are hydrogen or C_1 to C_4 alkyl;

wherein R_8 and R_9 may be the same or different and are hydrogen or C_1 to C_4 alkyl;

wherein R_{10} and R_{11} may be the same or different and are azido, halogen, hydroxyl, sulfamoyl (H_2NSO_2O), C_1 to C_4 alkoxy, C_1 to C_4 alkyl thiocarbonate (RSC(O)O), C_1 to C_4 alkyl carbonate (ROC(O)O), or C_1 to C_4 alkyl carboxylate (RC(O)O), wherein R is C_1 to C_4 alkyl,

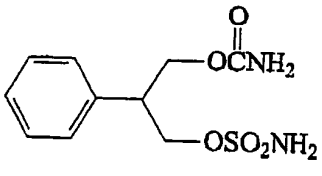


(Formula III)

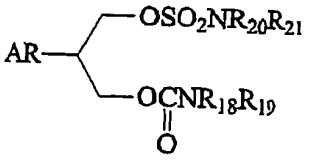
wherein R_{12} and R_{13} may be the same or different and are hydrogen, alkyl (C_1 to C_6), cycloalkyl (C_3-C_7), allyl, or benzyl;

R_{14} and R_{15} are the same or different and selected from hydrogen or lower alkyl; and

X_2 may be chosen from carbon (C) or sulfur (S), with the stipulation that when X_2 is carbon, R_{16} and R_{17} are the same or different and are selected from hydrogen or lower alkyl, whereas when X_2 is sulfur one of R_{16} and R_{17} is oxygen and the other is a lone pair of electrons or both R_{16} and R_{17} are oxygen,

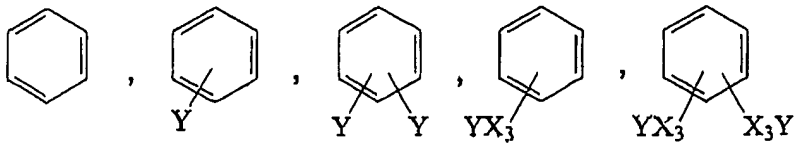


(Formula IV), and



(Formula V)

wherein, AR is represented by the following formulas;



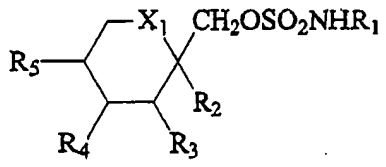
Y is selected from the group consisting of halogens, trifluoromethyl and alkyl groups containing 1 to 3 carbon atoms when Y alone is attached to the benzene ring; or

when X_3, which may be S or O, is present, Y is selected from the group consisting of trifluoromethyl and alkyl groups containing 1 to 3 carbon atoms; and

R_{18}, R_{19}, R_{20}, and R_{21}, may be identical or different and are selected from the group consisting of hydrogen, linear or branched alkyl groups containing 1 to 16 carbon atoms, cyclic alkyl groups containing 3 to 16 carbon atoms and aryl groups containing 6 to 8 carbon atoms, and $NR_{18}R_{19}$ and $NR_{20}R_{21}$, which may be identical or different, each may form a 3 to 7-membered aliphatic cyclic compound together with another nitrogen atom or oxygen atom.

6. A method for promoting wound healing comprising the administration of a therapeutically effective amount of a composition comprising an anti-convulsant agent and a carrier.

7. The method according to claim 6, wherein said anti-convulsant agent is selected from the group consisting of:



(Formula I)

wherein

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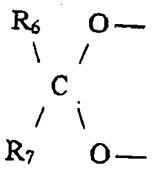
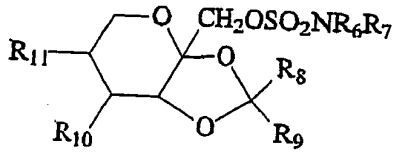
R_1 is hydrogen or alkyl; and

R_2, R_3, R_4, and R_5 are independently hydrogen or lower alkyl and, R_2 and R_3 and/or R_4 and R_5 together may be a methylenedioxy group of the following formula:



wherein R_6 and R_7 are the same or different and are hydrogen, lower alkyl or are alkyl and are joined to form a cyclopentyl or cyclohexyl ring,

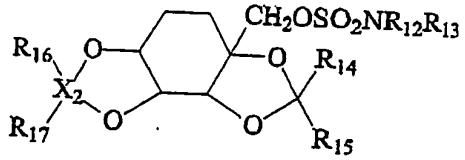


(Formula II)

wherein R_6 and R_7 may be the same or different and are hydrogen or C_1 to C_4 alkyl;

wherein R_8 and R_9 may be the same or different and are hydrogen or C_1 to C_4 alkyl;

wherein R_{10} and R_{11} may be the same or different and are azido, halogen, hydroxyl, sulfamoyl (H_2NSO_2O), C_1 to C_4 alkoxy, C_1 to C_4 alkyl thiocarbonate (RSC(O)O), C_1 to C_4 alkyl carbonate (ROC(O)O), or C_1 to C_4 alkyl carboxylate (RC(O)O), wherein R is C_1 to C_4 alkyl,



(Formula III)

wherein R_{12} and R_{13} may be the same or different and are hydrogen, alkyl (C_1 to C_6), cycloalkyl (C_3-C_7), allyl, or benzyl;

R_{14} and R_{15} are the same or different and selected from hydrogen or lower alkyl; and

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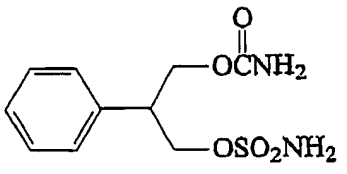
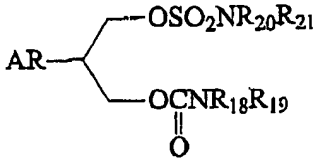
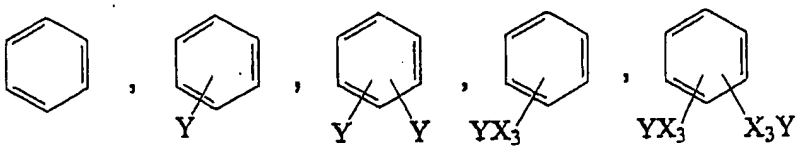


(Formula IV), and



(Formula V)

wherein, AR is represented by the following formulas;



Y is selected from the group consisting of halogens, trifluoromethyl and alkyl groups containing 1 to 3 carbon atoms when Y alone is attached to the benzene ring; or

when X_3, which may be S or O, is present, Y is selected from the group consisting of trifluoromethyl and alkyl groups containing 1 to 3 carbon atoms; and

R_{18}, R_{19}, R_{20}, and R_{21}, may be identical or different and are selected from the group consisting of hydrogen, linear or branched alkyl groups containing 1 to 16 carbon atoms, cyclic alkyl groups containing 3 to 16 carbon atoms and aryl groups containing 6 to 8 carbon atoms, and $NR_{18}R_{19}$ and $NR_{20}R_{21}$, which may be identical or different, each may form a 3 to 7-membered aliphatic cyclic compound together with another nitrogen atom or oxygen atom.

8. The method according to claim 6, wherein said composition comprises a salve, ointment, aerosol, cosmetic, or bioadhesive.

9. The method according to claim 6, wherein said composition is administered as a component of a bandage, transdermal patch, wound dressing, cosmetic, or bioadhesive.

10. The method according to claim 8, wherein said composition is a component of a bandage, wound covering, or wound dressing.

11. The method according to claim 1, wherein the therapeutically effective amount is about 0.1 to 400 mg.

12. The method according to claim 1, wherein the therapeutically effective amount is about 10 to 200 mg.

13. The method according to claim 1, wherein the therapeutically effective amount is about 25 mg.

14. The method according to claim 5, wherein the therapeutically effective amount is about 0.1 to 400 mg.

15. The method according to claim 5, wherein the therapeutically effective amount is about 10 to 200 mg.

16. The method according to claim 5, wherein the therapeutically effective amount is about 25 mg.